CINCINNATI VETERANS' AFFAIRS MEDICAL CENTER CINCINNATI, OHIO

HUMAN RESEARCH PROTECTION PROGRAM STANDARD OPERATING PROCEDURES

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CINCINNATI VETERANS AFFAIRS MEDICAL CENTER
RESEARCH SERVICE STANDARD OPERATING PROCEDURES
FOCUSING ON THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

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0100 Introduction

The purpose of these Standard Operating Procedures (SOPs) is to establish functions, responsibilities, institutional relationships, and membership of the Research Service as it serves the Cincinnati VA research community, and to aid investigators in the process of conducting human subjects research under the authority and auspices of the VA Hospital. These SOPs are based on Department of Veteran's Affairs (VA), Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), and other Federal, State, and institutional regulations and policies. **NOTE: All UC IRB policies and procedures relating to the protection of human subjects can be found at the UC IRB website at http://researchcompliance.uc.edu or by calling the UC IRB office at (513) 558-5259.**

The Research Service, located in the Cincinnati Veterans Affairs Medical Center (Cincinnati VA), supports the hospital's efforts to provide high quality health care to veterans through its support and coordination of clinical, animal, laboratory, and other research. The Research and Development (R&D) Committee, in cooperation with the Research Service, reviews and monitors all human subjects research, including clinical trials research, medical records reviews, and human tissue studies.

The Research Service also administers laboratory research, much of which involves the use of animals. The Animal Research Committee oversees investigations using animals. This committee reviews and monitors all animal care and use in research that involves VA Hospital researchers, facilities, and/or VA funding.

The Research Service has close ties with the University of Cincinnati and the UC Hospital and Clinics. The Research Service works closely with UC Institutional Review Boards (IRBs) and the UC Institutional Animal Care and Use Committee (IACUC).

A major responsibility of the Cincinnati VA Research Service is to ensure the protection of every research participant within the limits of the uncertainties inherent in research. **It is the responsibility of the Medical Center Director to ensure that (1) each VA medical center conducting research involving human participants has a systematic and comprehensive approach to ensure the protection of human participants participating in VA approved research. (2) They must also ensure that this system, known as the Human Research Protection Program, is composed of a number of individuals, offices, committees and subcommittees. (3) The exact composition of the HRPP is dependent on the specific facility, the resources of the facility, and the size and complexity of the research program at the facility. (4) The medical center director must ensure effective coordination by and among the various individuals, offices and committees that comprise the Human Research Protection Program. (5) Every VA medical center conducting research involving human participants or human biological specimens applies through the Office of Research Oversight to DHHS, OHRP for an Assurance of**

Compliance and must obtain this Assurance prior to conducting any such research. (6) Every VA medical center conducting research involving human participants has an established or designated IRB. (7) Adequate administrative support, including personnel and space sufficient to provide privacy for conducting sensitive duties and storage of records, is provided for IRB activities. (8) The VA medical center must also provide appropriate educational opportunities for IRB members and staff, and for researchers. (9) Developing and monitoring procedures to ensure the safety of participants in research either directly or by delegating the responsibility to other qualified VA staff. (10) The local research office maintains accurate, up-to-date records regarding the mandatory training and credentialing of investigators and other appropriate research staff in the protection of human research participants. (11) This is required by the Office of Research and Development. (12) The medical center director is responsible for the oversight of both the IRB and all VA investigators (compensated, WOC, or IPA) (13) Responsible for the assurance that IRB members and investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and all applicable regulations. (14) The MCD is responsible for the development and implementation of an educational plan for IRB members, staff and investigators.

The Medical Center Director must be the Institutional Official for all assurances and must fulfill all educational requirements mandated by VA Office of Research and Development, the facility's assurance, funding institutions, and OHRP.

It is the responsibility of all employees, Principal Investigators, and their Research Staff to protect the patients and respect their rights during research, investigation and clinical trials involving human subjects. The Service is therefore committed to promoting the conduct of research in compliance with all applicable laws and regulations in a manner that protects the human subjects involved. To ensure this, the Research Service has published these Standard Operating Procedures (SOP) to assist the Cincinnati VA research community in implementing the Human Research Protection Program (HRPP).

Establishing an appropriate research environment requires an ongoing effort to educate researchers, their staff, research administrators, IRB members, VA R&D Committee members, institutional officials, and study participants about research ethics and other HRPP issues. This document is part of the effort to ensure an ethical research environment including accountability, ethics training, transparency, and open communication. This SOP will be reviewed and approved by the Research and Development Committee annually, within the first quarter of the new calendar year. If modifications to the SOP are needed throughout the year, they will be reviewed and approved from the R&D Committee also.

All modifications of our policies and procedures will be e-mailed to the study personnel distribution lists after R&D approval of those modifications. The Cincinnati research

website (www.cincinnati.research.med.va.gov) will be updated within 5 business days after committee approval.

0200 Authority for these Policies and Procedures

- VHA Handbook 1200.5, R&D Policy Directive, M-3, Part 1, Chapters 2 and 3
- VHA Pharmacy Manual, M-2, Part VII, Chapter 6 and Chapter 5.10
- Statutory provision for protection of VA patient rights (38 USC Sections 501, 7331)
- VA regulations pertaining to protection of patient rights (38 CFR 17.33a and 17.34)
- VA regulation pertaining to rights and welfare of human subjects participating research (38 CFR 16 - Federal Policy for the Protection of Human Subjects – The Common Rule)
- VA regulations pertaining to research related injuries (38 CFR 17.85)
- VA regulations pertaining to hospital care for research purposes and outpatient care for research purposes (38 CFR 17.45, 17.92)
- Statutes and regulations pertaining to the release of patient information (5 USC § 522a; 38 USC §§ 5701a, 7332; 45 CFR Parts 160-164)
- Department of Health and Human Services (DHHS) regulations pertaining to rights and welfare of human subjects participating in research supported by DHHS (45 CFR 46)
- Food and Drug Administration (FDA) regulations pertaining to rights and welfare of human subjects participating in research involving investigational drugs and devices (21 CFR parts 11, 50, 56, 312, 812, and 814)

0300 What Constitutes Research at the Cincinnati VA

All research involving human subject conducted at the CVAMC or by CVAMC employees or agents on VA official time must be reviewed by the UC IRB. Sometimes questions arise as to whether an activity is considered human subject research. This chapter is intended to provide a reference to assist investigators in determining when an activity is human subject research. When in doubt, investigators should contact the IRB Office.

All human subject research including research that qualifies as exempt from IRB review must be submitted to the affiliate IRB office for review by the IRB Chairperson or the IRB Vice-Chairperson.

The following definitions are provided to assist in determining is the work being performed is considered Human Subject Research.

VA Definitions: VA regulations at 38 CFR 16.102(d), Cincinnati VA Medical Center Memorandum 151-15 and the Common Rule defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

VA regulations at 38 CFR 16.102(f) and the Common Rule define human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information." VA policy at VHA Handbook 1200.5(3.g) clarifies that human subjects may also include investigators, technicians, and other assisting investigators when they serve a "subject" role by being observed, manipulated, or sampled when the activity is determined to be research.

FDA Definitions: FDA regulations at 21 CFR 56.102(c) define research as "any experiment that involves a test article and one or more human subjects." FDA regulations note that "[t]he terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part."

FDA regulations at 21 CFR 56.102(e) define human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."

Private Information. Federal regulations define private information to include any information that an individual can reasonably expect will not be made public, and any information about behavior that an individual can reasonably expect will not be observed or recorded.

Identifiable. Federal regulations define identifiable to mean that the identity of the individual subject is or may readily be ascertained by the investigator or associated with the information.

Minimal Risk. Federal regulations at 45 CFR 46.102(f) and 21 CFR 56.102(i) define minimal risk to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minimal Risk for Prisoners. In the case of research involving prisoners, federal regulations at 45 CFR 46.303(d) define minimal risk as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Institutional Review Board (IRB). An IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the Common Rule, DHHS regulations, and FDA regulations, the IRB has responsibility for approving, requiring modification in (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common

Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

Types of Human Subject Research. The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research.

Biomedical Research. Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of Biomedical Research.

Social and Behavioral Research. The goal of Social and Behavioral Research is similar to that of Biomedical Research—to establish a body of knowledge and to evaluate interventions—but the content and procedures often differ. Social and Behavioral Research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.

Clinical Research. Clinical research involves the evaluation of biomedical or behavioral interventions related to disease processes or normal physiological functioning. Clinical research often, but not always, includes drugs, devices, or biological products regulated by the Food and Drug Administration (FDA).

Epidemiology Research. Epidemiology research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, interventions, or delivery of services to affected populations. Some epidemiology research is conducted through surveillance, monitoring, and reporting programs—such as those employed by the Centers for Disease Control and Prevention (CDC)—whereas other epidemiology research may employ retrospective review of medical, public health, and/or other records. Because epidemiology research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may quality for exemption or expedited review. In all cases, the IRB, not the individual investigator, will determine when IRB review of the activity is required. (Please refer to the UC IRB website at http://researchcompliance.uc.edu/ or contact the UC IRB office at (513)-558-5259)

Repository Research, Tissue Banking, and Databases. Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB

review. When data or materials are stored in a bank or repository for use in future research, the IRB must review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols. New projects must utilize VA-sponsored tissue banks (VHA Directive 2000-043 "Banking of Human Research Subject's Specimens").

Pilot Studies. Pilot studies involving human subjects are considered human subject research and require IRB review.

Human Genetic Research. Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that "third parties," about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with 38 CFR 16.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

Quality Assurance Activities vs. Human Subject Research. Quality Assurance activities attempt to measure the effectiveness of programs or services (e.g., medical use evaluations (MUEs) conducted by Pharmacy personnel.) Quality Assurance activities constitute human subject research (when involving participants), and require IRB review, when they are designed or intended, at least in part, to develop or contribute to generalizable knowledge.

On the other hand, Quality Assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, usually do not constitute human subject research, and usually do not require IRB review.

For example, suppose one of the CVAMC Sections conducts a review of patient records and then contacts patients to identify cases where recommended follow-up did not occur. If the sole intent is to improve the rate of follow-up at CVAMC, then the activity is not human subject research and does not require IRB review. However, if the intent of the activity, at least in part, includes extending the findings to patients at facilities outside CVAMC, or disseminating the findings in such a way that applicability outside CVAMC is stated or implied, then the activity does constitute human subject research, and does require IRB review.

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal CVAMC purposes lead to a desire to generalize and disseminate the results for application outside CVAMC), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

Where any disagreement arises about whether a Quality Assurance activity constitutes human subject research, the IRB, not the individual investigator, will determine when IRB review of such activities is required.

Research Activities vs. Innovative Treatments in Medical Practice. In the course of medical practice, sound clinical judgment sometimes leads physicians to employ "innovative" treatments where more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient's individual needs. Such innovative treatments employed on an occasional basis and solely for clinical purposes do not normally constitute human subject research and do not normally require IRB review.

However, the use of innovative treatments as part of a systematic investigation designed, at least in part, to develop or contribute to generalizable knowledge does constitute human subject research and does require prospective IRB review.

Research Activities vs. Medical Case Reports. Generally speaking, a case report is not usually considered research because it is not usually "a systematic investigation designed to develop or contribute to generalizable knowledge" therefore it does not come under the rubric of the IRB or R&D Committee. Further, the case report presentation, whether by lecture or publishing, is executed by the physician of record, meaning that the patient's own physician is reporting the case and already has identified the patient and has access to the clinical data. If the presentation uses photographs, initials, or any other information that may possibly

identify the patient, then written permission or a separate consent form for this purpose is required.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review and then requires IRB approval. Usually, a (non-research) case report summarizes one case (or occasionally two, or at most three, cases) to emphasize a discrete instance of disease. However, it is the nature of the report, not the absolutely number of cases, that determines whether or not the activity involves human subject research. A non-research case report may not involve a systematic investigation characterized as developing or contributing to generalizable knowledge. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subjected to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A (non-research) case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at a least a systematic qualitative analysis, that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

Research Activities vs. Commercial Services. CVAMC facilities and laboratories may occasionally provide tests or other services to non-CVAMC researchers solely on a commercial basis (e.g., CVAMC performs MRIs for non-CVAMC investigators solely on a commercial basis).

Provision of such services solely on a commercial basis does not constitute CVAMC human subject research and does not require UC IRB review, provided that all of the following conditions are met:

- **The research is not otherwise conducted at CVAMC;**
- **The research does not otherwise involve CVAMC employees or agents (e.g., as co-investigators, in planning or analysis, or receiving publication credit);**
- **The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges;**
- **The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality; and**
- **The commercial services are conducted under a valid contract.**

However, if CVAMC personnel are involved in any way that is more than merely providing a commercial service, then prospective review and approval of the UC IRB is required.

For Policies and Procedures regarding IRB determinations of Human Subjects Research you can log onto their website at www.researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259.

0301 The Cincinnati VA Human Subject Research Purview

Research is under the VA R&D Committee purview if:

1. It is conducted completely or partially in VA facilities or at approved off-site locations/facilities
2. It is conducted by researchers with VA appointments while on official VA duty (including those with WOC ["without compensation"] status) or
3. If the research involves veterans associated with the Cincinnati VA Medical Center or its satellites (i.e., if they are patients of, or otherwise receive treatment from, VA clinics or physicians)

The research may be VA funded, funded from extra-VA sources, or conducted without direct funding.

All clinical trials and other human subjects research, or research that involves medical records or databases, human tissue, or otherwise derives its data from intervention or interaction with human subjects, must be reviewed by both the VA R&D Committee, and either University of Cincinnati IRB I or II. Research will be reviewed to help ensure that it is scientifically sound, ethical, minimizes risk, maintains confidentiality, and minimizes financial conflict of interest. Approval must be attained from both the R&D Committee and the IRB prior to the initiation of a study.

0302 Limits on Human Subject Research at the Cincinnati VA

Research that is not permitted at the Cincinnati VA includes:

1. research related to *in vitro* fertilization
2. research using prisoners as subjects*
3. research using children as subjects*
4. research involving human embryonic stem cells

(*The prohibitions on research with children or prisoners may be waived by special dispensation from VA Central Office. *In vitro* and embryonic stem cell prohibitions cannot be waived.)

Some research may be considered to be of questionable appropriateness to the Cincinnati VA:

1. research whose sole purpose is to help students fulfill degree requirements
2. projects which are unlikely to contribute to general knowledge
3. research that would unduly strain the patient care mission of the VAH or unduly inconvenience or embarrass VA patients

4. research that would consume inordinate amounts of VA resources

No research involving human subjects may be undertaken without both R&D Committee AND IRB review and documented approval, or approval of an exemption.

0303 The Human Research Protection Program (HRPP)

The Research Service shall work within a systematic HRPP designed to ensure the rights, safety, and well being of veteran and other patients/subjects in relation to their participation in VA research activities. The program shall consist of a comprehensive system of rules, documents, processes, and people to protect participating human subjects.
The HRPP shall be concerned with the creation, acquisition, use, and disclosure of information between individuals and entities engaged in or regulating human subjects research. Use is considered the sharing, employment, application, utilization, examination or analysis of information within the VHA. Disclosure is the release, transfer, provision of access to, or divulging in any manner information outside the VHA.

Under the HRPP system, human subject research activities at the VA shall be guided by the ethical principles as outlined in the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki, (Appendix 2.c, 2.d, 2.e, respectively) and as described in the Common Rule (Appendix 2.a,b).

The essential functions of the HRPPP shall include:

1. comprehensive review of protocols
2. ethically sound participant-investigator interactions
3. ongoing (risk appropriate) safety monitoring
4. quality improvement / compliance activities
5. education and training of investigators and research staff (see section 1100)

A variety of individuals and committees are all a part of, or contribute to, the VA HRPP program, including:

1. Medical Center Director (Institutional Official)
2. Chief of Staff
3. Associate Chief of Staff for Research (ACOS/R)
4. Administrative Officer for Research (AO/R)
5. Compliance Officers
6. R&D Committee
7. UC Medical Center IRBs and their staff
8. Other committees or subcommittees (e.g., Subcommittee on Research Safety, Radiation Safety, Oversight Committee, Conflict of Interest)
9. Investigators/Researchers
10. Research staff

11. Health and safety staff
12. Research pharmacy staff
13. Research Service Administration Staff
14. Other personnel concerned with patient safety and privacy

The objective of the HRPP system shall be to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

0303.1 Federalwide Assurance

The Federalwide Assurance (FWA) became effective on August 20, 2003, was renewed January 30, 2006 and will expire on January 29, 2009, the number is FWA-00005399. Investigators at the Cincinnati Veterans Affairs Medical Center are covered by this University of Cincinnati FWA through a Memorandum of Understanding (MOU) with the University. The FWA is an agreement between the University, this VA Hospital, the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the Department of Veterans Affairs, Office of Research Oversight (VA ORO), that is designed to support the HRPP and is built on the assumption that the VA hospital as an institution is accountable for the protection of human research subjects when engaging in its research mission.

The assurance formalizes the Cincinnati VA Medical Center's commitment to protect human subjects participating in research. The assurance states that the VA Hospital is responsible for compliance with human research protection regulations as described in the Federal Policy for the Protection of Human Subjects, known as the Common Rule and will be guided by the ethical principles found in the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research). The assurance grants the VA hospital the authority to hire or appoint, train, supervise and discipline investigators. It is responsible to assure the scientific merit of the research conducted within the institution and to assure that human research subjects are protected. The assurance states that the Cincinnati Veterans Affairs Medical Center shall utilize an IRB in the review of research. The IRB, in turn, shall assure that the research protects human subjects and meets regulatory requirements. The VA Medical Center, as part of this assurance function, must conduct reviews of compliance and continuous quality improvement of its HRPP functions. In short, this facility shall operate a comprehensive and organized system to protect those who participate as subjects in its research.

The Medical Center Director is the official responsible for maintaining the assurance. The Research and Development (R&D) Committee is responsible

for ensuring that the HRPP is operational.

0303.2 Memorandum of Understanding

The Memorandum of Understanding (MOU) is the agreement between the VA Medical Center and the University of Cincinnati concerning the VA's utilization of the University's Institutional Review Boards regarding the protection of human subjects in research. The MOU establishes the terms of the cooperative agreement between these two entities. According to the MOU, neither the VA medical center nor the University may enter into collaborative human research with VA support with an institution that does not hold a Federal Wide Assurance or its equivalent. The Cincinnati VA Medical Center follows all state and federal regulations. The MOU is attached as Appendix 4.

0303.3 Quality Assurance & Quality Improvement

As part of the Human Research Subject Protection Program (HRPP), in keeping with the VA's commitment to high quality in research, to best protect human subjects, and to maintain compliance with all applicable regulatory guidelines, there shall be a Quality Assurance/Quality Improvement (QA/QI) component to the activities of the Research Service, the Health Sciences Institutional Review Boards (IRBs), and the VA Research and Development (R&D) Committee.

The goals of the QA/QI Program are:

1. To enhance the protection of human subjects who participate in research programs under the purview of the Cincinnati VA Medical Center;
2. To ensure compliance with the Federal-Wide Assurance (FWA), the Memorandum of Understanding (MOU) between the Cincinnati VA and the University, VA and other federal regulations, state laws, and ethical guidelines for human subjects research;
3. To encourage continuous improvement in the conduct of human research at the Cincinnati VA;
4. To promote an institutional culture of responsible research and cooperation between the Research Service and investigators to improve the quality of research;
5. To provide the institution with information about the quality of clinical research;
6. To proactively address potential issues and provide guidance in their resolution; and
7. To offer research teams an opportunity to learn through external evaluation.

To meet these goals, on an annual basis, the Research Compliance Officer will present a report to the R&D Committee will assess its performance, and that of its subcommittees, including the IRB, with regard to compliance with

established policies and procedures. By appropriate audits or reports, there shall be a determination of the Cincinnati VA's compliance with research subject protection requirements and assurance that all committees are fulfilling their role in meeting the program objectives. This assessment will also include review and evaluation of the reports and results of compliance assessment and quality improvement activities concerning the HRPP.

R&D Committee **and/or its delegated subcommittee** activities designed to assess the HRPP will include, but not be limited to:

1. Updating the Human Subjects Standard Operating Procedures (this manual) as needed and making those updates available to researchers, IRB members, and R&D Committee members;
2. Conducting periodic audits of IRB composition, operational procedures, and compliance with applicable regulations where they concern VA protocols;
3. Conducting random, select and for-cause audits of protocols and procedures. Regulatory and subject binders, case report forms, source documents, and/or the consent process may be monitored;
4. Reviewing and evaluating of reports by the IRB related to VA research;
5. Implementing needed improvements, and follow-up of these actions, as appropriate;
6. Providing continuing education to R&D Committee members, and investigators.

0303.4 Support of the HRPP

It is important that the HRPP be provided with adequate resources, which may include funds and/or facilities, and it is the responsibility of the R&D Committee to assure this.

One possible source of HRPP support is hospital funds and facilities. A second possible source is a fee levied on industry-supported grants rect costs for that portion of research conducted at the Cincinnati VA Medical Center, which ever is greater. This fee can be reduced by the R&D Committee in special circumstances.

The ACOS/R will:

1. Verify that the entity which administers industry-supported research funds is aware of this policy (the two principal entities are the Cincinnati Foundation for Biomedical Research and Education (CFBRE), and the University of Cincinnati (UC).
2. Obtain an annual account of the total amount of direct costs of industry-funded studies supporting research conducted at this medical center, as well as the amount of funds that were made available for support of HRPP costs.

The Research Service shall annually report the following to the CFBRE Board of Directors and the Office of Research and Development (ORD):

1. Information received from the entity administering the study funds, and
2. An accounting of all expenditures in support of compliance-related activities

0400 The VA Research and Development Committee and the IRB

Both the VA Research and Development Committee and the IRB shall review, or grant exemption from review, all proposed research involving human subjects conducted under the purview of the VA Research Service, regardless of the source of funding. Prior to initiation of a research project, both bodies must grant approval and the written approval must be received by the investigator. The R&D Committee may not overrule a disapproval, suspension, or termination decision of the IRB.

The Research and Development Committee will be responsible for ensuring periodic evaluation of whether the number of IRB's was appropriate to the volume and types of human research reviewed, so that reviews were accomplished in a thorough manner.

0500 The VA Research and Development (R&D) Committee

The R&D Committee is the local committee charged with oversight of all R&D activities within the Cincinnati Veterans Affairs Medical Center. At each meeting, a quorum must be present constituting a majority of the voting members. The R&D Committee shall meet at a minimum of 11 months annually.

The R&D Committee members should report undue influence to the ACOS/Research, the RCO and the Medical Center Director. If the ACOS/R and or RCO become privy to reports of undue influence by the R&D Committee members, they will inform the Medical Center Director within 24 hours. The ACOS/Research and/or the Medical Center Director will work with the RCO to investigate the allegations and take corrective action.

0501 Function of the VA R&D Committee

The primary purposes of the R&D Committee are to:

1. Help maintain high scientific standards throughout the VA R&D program.
2. Assure that the research conducted at the Cincinnati VA is consistent with the broad objectives of the VHA and its research program and supports the patient care mission of the facility.
3. Evaluate the quality, appropriateness, and feasibility of research proposals
4. **Determine the study design and procedures to be consistent with sound research design, which did not unnecessarily expose participants to risk.**

5. Review research protocols in light of human subject protection, research personnel safety, and the considerations listed above (1-4).
6. Review the research facilities available at the Medical Center to assure that they are of continuing high quality to support the R&D program.
7. Recommend the distribution of R&D funds, space, personnel, supplies, equipment and use of animal facilities and other common resources when these issues are brought to the attention of the committee.
8. Advise the Associate Chief of Staff for Research (ACOS/R) and the Medical Center Director on professional and administrative aspects of the R&D program.
9. Oversee the operations of subcommittees charged with evaluating human research, animal welfare and research safety; this oversight will include items mentioned above (0303.3).
10. Review reports of complaints, allegations of research non-compliance or improprieties, and research QA/QI activities.
11. Set institutional policy for training of research personnel.

The VA R&D Committee shall have access to all records and shall review minutes of the IRB reviews of VA protocols. The VA R&D Committee may not alter the minutes of any sub-committee. The R&D Committee and the Research Service agrees to maintain the confidentiality of all records the UC shares with them related to the IRB review of research protocols. The Research Service shall develop a file for each approved protocol and maintain a copy of the proposal with all amendments, and copies of all date-stamped consent forms. The Research Service shall be responsible for maintaining accurate, up-to-date records regarding the mandatory training and certification of investigators and research staff in the protection of human subjects. The Research Service will keep on file any communications or notifications to investigators that originate from R&D Committee actions related to the research. Other study related documentation shall be kept on file by the IRB with R&D Committee access.

The ACOS/R shall review all Adverse Event (AE) reports, Data Safety Monitoring reports, auditing or monitoring reports provided by investigators and the IRB on VA protocols. The ACOS/R will report on these to the R&D Committee. A more thorough review will be done of those reports deemed significant by either the ACOS/R or the R&D Committee.

0502 R&D Committee Composition

The membership of the R&D Committee shall consist of at least 12 representatives appointed by the Medical Center Director or delegate from the following categories:

1. At least four members are selected because they have direct patient care responsibilities and/or expertise in clinical research
2. At least two members are chosen because they have expertise in basic

science research
3. At least one member shall be selected to represent the Nursing Service and/or UC College of Nursing
4. Whenever possible, one member of the committee with expertise in biostatistics and research design
5. The members should have diverse backgrounds and shall include at least one non-physician
6. These qualifications may overlap so that, for example, the UC representative may also have expertise in biostatistics
7. One member is chosen to represent the Ethics Committee
8. Three members are selected to represent the Dean's Committee
9. All Research involving FDA regulated articles must be reviewed in a meeting where quarum includes a licensed physician.
10. Members usually serve for a term of three years, but this may be extended if it benefits the Committee. Members who have expertise needed by the Committee but have other heavy time commitments, may share a membership with a colleague who has similar expertise.

0502.1 <u>Special Personnel on the R&D Committee</u>

The Director of the Cincinnati VA Hospital is the institutional official responsible for all aspects of the research program of the local VA facility.

The R&D Committee is appointed by and is responsible to the Director, for maintaining the quality and meeting the objectives of the research program.

The Director, the Medical Center Chief of Staff, Administrative Officer for Research (AO/R), the Veterans Service Organization (VSO) representative and the Research Compliance Officer (RCO) serve as *ex officio* non-voting members.

The Associate Chief of Staff for Research (ACOS/R) is the delegated authority for management of the R&D program and is responsible for administering the operations of the R&D Committee. The ACOS/R serves as the Executive Secretary of the Committee and has a vote on the committee.

The Administrative Officer for Research (AO/R) serves as a non-voting member.

VA legal representative is available for counsel as a legal subject matter expert.

0502.2 Conflicts of Interest for R&D Committee Members

The same standards for dealing with potential conflicts of interest that are described for IRB members in section 0602.1 will apply to R&D Committee members.

0502.3 R&D Committee Training

All R&D Committee members shall be provided with orientation by the ACOS/R and/or RCO about the Research and Development Program of the Department of Veterans Affairs, the mission of the VA R&D Program and the values that guide all R&D efforts. Because of the Committee's role in the protection of human subjects as part of the VA hospital's Human Research Protection Program, members are required to complete training in human studies protection and Good Clinical Practices (see 1300: Research Team Training). In addition, for on-going training and education, new information on VA research guidelines, research protection (human and animal subjects, safety) issues, etc., shall be reviewed and discussed by the Committee.

0502.4 R&D Subcommittees

The R&D Committee is supported by specialized subcommittees that meet on a scheduled basis. Each subcommittee shall keep minutes of its meetings and report its actions or recommendations to the R&D Committee in a timely manner. If a project needs subcommittee approval, it must be approved by the relevant subcommittees and receive final approval from the R&D Committee before being conducted. The R&D Committee may accept or overrule actions or recommendations of a subcommittee, except decisions by the IRB to disapprove, suspend, or terminate a study. The R&D Committee may require a modification to a protocol to secure R&D approval on studies that have previously received IRB approval. These modifications would require submission and approval by the IRB prior to receiving final approval from the R&D.

The Subcommittees and related committees include:

1. IRB – as described below, the IRB utilized by the Cincinnati VA is an affiliate entity that is part of the UC system Research Safety
2. Subcommittee on Research Safety (SRS)
3. Institutional Animal Care and Use Committee (IACUC)
4. General Clinical Research Center Scientific Advisory Committee GCRC-SAC

0503 R&D Committee Meeting Minutes

Minutes shall be recorded and maintained for each meeting of the R&D Committee.

The minutes shall:

1. Document attendance or absence of members and provide a complete record of all items of business or information brought before the Committee.
2. Record verbatim motions presented to the Committee and document the action taken by the Committee, including the number of members voting for, against, or abstaining (from) the motion.
3. Note recusals due to possible conflict of interest.
4. Be signed by both the Chair and the ACOS for Research and then forwarded to the facility Director and the Chief of Staff.
5. Minutes shall also be reviewed by the Clinical Executive Board (CEB).
6. Prior to the next meeting, copies of the minutes, together with any comments by the Director, will be distributed to all members of the Committee. The minutes will be reviewed and approved, with edits as necessary, by the Committee.
7. Within five weeks after the meeting, the approved minutes will be made available upon request to any investigator and copies will be forwarded through appropriate channels to VA Central Office (VACO) if so directed by the Chief Research and Development Officer (CRADO).

0504 R&D Committee Meeting Agendas

The Research Service in consultation with the chair prepares meeting agendas for the R&D Committee meeting. The agenda shall note the scheduled date, time and location of the meeting.

The following shall be included in the R&D Committee meeting agenda:

1. Training/continuing education.
2. Reviews of minutes of last R&D meetings, and of subcommittee meetings. This may include reports from subcommittee chairs or VA member of IRB.
3. Reports and announcements (reports shall be made by the chair, ACOS/R, AO/R, RCO and/or any other responsible individual on matters of concern to the research program).
4. Compliance and assurance information.
5. Initial review of new research protocols.
6. Review of amendments to ongoing or previously approved protocols.
7. Review of protocols previously deferred.
8. Report on previously reviewed items for which changes required could be confirmed under expedited review procedures.
9. Report of items approved directly under expedited review procedures.
   (For each expedited review, note the following: the reviewer, date reviewed, and action taken. Items reviewed under expedited

procedures but not approved are entered on the agenda in the category that would be appropriate if the expedited review had not been conducted)

10. Reports by the ACOS/R on adverse events, data safety monitoring, and other significant protocol-specific issues
11. Summaries of Research Compliance and QA/QI Reports
12. Other business

0505 R&D Committee Maintenance of Written Procedures of Operations

The operations of the R&D Committee shall comply with written standard operating procedures (this document) and other official VA policies and procedures in order to ensure the proper conduct of high quality research within the Cincinnati VA Medical Center. All persons involved with the research program, including all committee and subcommittee members, research administrative staff, research investigators, research study coordinators and research study assistants, shall be informed of these SOPs for appropriate compliance.

0600 The HRPP Oversight Committee

The primary purposes of the Oversight Committee is to ensure the rights, safety and well being of human subject participants in VA approved research activities. The committee will assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects.

0601 Function of the HRPP Oversight Committee

The HRPP Oversight Committee will be responsible for:

1. **Implementing the institution's HRPP Standard Operating Procedures.**
2. **Reviewing and evaluation the reports and results of compliance assessment and quality improvement activities (QA/QI) related to research.**
3. **Implementation of needed improvements and follow-up on actions, as appropriate.**
4. **Review, on an annual basis, the investigational device control sheet, containing information on the storage, security and dispensing of the device of an approved study.**
5. **Provide periodic review of Investigational Drug Pharmacy files.**
6. **Assisting in the investigation of complaints and allegations.**
7. **Monitoring the response to each complaint and allegation as needed.**
8. **Assisting in the pre-screening interview as necessary.**
9. **Confirming that the individual's required to have education and training by VA and Federal requirements have met requirements on an annual**

basis.

10. **Periodically evaluating Research outreach activities and initiating changes when appropriate.**
11. **Fulfilling such other functions as may be specified by the Medical Center Director.**

0602 Oversight Committee Composition

The membership of the Oversight Committee shall consist of at least 7 representatives appointed by the Medical Center Director or delegate from the following categories:

1. **The Research Compliance Officer shall act as the chair of the committee**
2. **The Research Service Program Analyst**
3. **At least two members are chosen because they have expertise in human subject research**
4. **At least one study coordinator experienced in Human Subject Research**
5. **At least one member shall be selected to represent the Investigational Drug Pharmacy**
6. **One representative from the Institutional Review Board (IRB)**
7. **One representative from the Medical Center Office of Quality Management**
8. **One representative from the R&D Committee**
9. **These qualifications may overlap so that, for example, the IRB representative may also have experience in Human Subject Research.**
10. **Members usually serve for a term of three years, but this may be extended if it benefits the Committee.**

0602.1 Special Personnel on the Oversight Committee

The Medical Center Director, Chief of Staff, ACOS/Research, the AO/Research serves as ex officio non-voting members

VA legal representative is available for counsel as a legal subject matter expert.

0602.2 Conflicts of Interest for Oversight Committee Members

The same standards for dealing with potential conflicts of interest that are described for R&D members in section 0502.2 will apply to Oversight Committee members.

0602.3 Reporting of Undue Influence Exerted Upon Committee Members

The Oversight Committee members should report undue influence to the ACOS/Research, the RCO and/or the Medical Center Director. If the ACOS/R and or RCO become privy to reports of undue influence by the Oversight Committee members, they will inform the Medical Center Director within 24 hours. The ACOS/Research and/or the Medical Center Director will work with the RCO to investigate the allegations and take corrective action.

0603 Oversight Committee Training

All Oversight Committee members shall be provided with orientation by the RCO about the Research and Development Program of the Department of Veterans Affairs, the mission of the Human Research Protection Program and the values that guide all R&D efforts. Because of the Committee's role in the protection of human subjects as part of the VA hospital's Human Research Protection Program, members (at a minimum) are required to complete training in Overview of Good Clinical Practices and Human Subjects' Protection (see 1100: Research Team Training). In addition, for on-going training and education, new information on VA research guidelines, research protection issues, etc., shall be reviewed and discussed by the Committee.

0604 Oversight Committee Meeting Minutes

Minutes shall be recorded and maintained for each meeting of the Oversight Committee.

The minutes shall:

1. **Document attendance or absence of members and provide a complete record of all items of business or information brought before the Committee.**
2. **Record verbatim motions presented to the Committee and document the action taken by the Committee, including the number of members voting for, against, or abstaining (from) the motion.**
3. **Note recusals due to possible conflict of interest.**
4. **Be signed by both the Chair and the ACOS for Research and then forwarded to the facility Director and the Chief of Staff.**
5. **Prior to the next meeting, copies of the minutes, together with any comments by the Director, will be distributed to all members of the Committee. The minutes will be reviewed and approved, with edits as necessary, by the Committee.**
6. **Within five weeks after the meeting, the approved minutes will be made**

available upon request to any investigator. All minutes will be maintained electronically and in hard copy (once signed by the Medical Center Director).

0605 Oversight Committee Meeting Agendas

The Program Assistance in consultation with the chair prepares meeting agendas for the Oversight Committee meeting. The agenda shall note the scheduled date, time and location of the meeting.

The following shall be included in the Oversight Committee meeting agenda:

1. **Reviews of minutes of last Oversight meetings, and of subcommittee meetings. This may include HRPP investigative reports prepared by the RCO or prepared by another source.**
2. **Reports and announcements (reports shall be made by the chair, ACOS/R, AO/R and/or any other responsible individual on matters of concern to the research program).**
3. **Compliance and assurance information.**
4. **Review of issues considered old business.**
5. **Review of any issues of non-compliance**
6. **Review summaries of Research Compliance and QA/QI Reports**
7. **Periodically evaluate Outreach Activities and suggest changes or additional services.**
8. **Other business**

0700 The University of Cincinnati Medical Center Institutional Review Boards (IRBs)

0701 Function of the IRB

The Cincinnati Veterans Affairs Medical Center has a Memorandum of Understanding (MOU) with the University of Cincinnati (hereafter called, "UC") concerning the use of the University's **Medical** IRBs (see section 0303.2 and Appendix 4)

The UC Medical Center Institutional Review Boards are charged with the responsibility to protect the rights and welfare of human subjects in research at, or conducted by faculty, staff, or students at the Cincinnati Veterans Affairs Medical Center, in addition to those at the UC. The IRB shall be part of an accredited HRPP through an accrediting organization whose standard of accreditation are at least equal to the organization approved by the VA (e.g. AAHRPP).

For UC IRB policies and procedures regarding the function of the IRB, please refer to the UC IRB website at http://researchcompliance.uc.edu or

call the UC IRB office at (513) 558-5259.

0702 IRB Maintenance of Written Procedures of Operations

Per the MOU with the University of Cincinnati, the IRB shall establish and provide to the VA Research Service written procedures including, but not limited to, those for:

1. Conducting its initial and continuing reviews of research and for reporting its findings and actions to the investigator and the R&D Committee
2. Determining which projects require review more often than annually and which projects need verification, from sources other than the investigator, that no material changes have occurred since previous IRB review
3. Ensuring that investigators promptly report proposed changes in a research activity including amendments to the protocol or the consent form to the IRB, and ensuring that such changes in approved research are not initiated without the IRB's review and approval except when necessary to eliminate apparent immediate hazard to the subject
4. Reporting of noncompliance by study personnel promptly to the IRB
5. Notifying hospital officials and the Research Service Office of adverse events and unanticipated problems involving risks to human subjects or others involved in VA research as required by VHA Handbook 1200.5, other VA policies, or other Federal regulations; instances of serious or continuing noncompliance with VA regulations or the requirements of determinations of the IRB; and suspension or termination of IRB approval
    a. The procedures shall indicate that the R&D Committee or Medical Center Director or designee shall, in turn, when required by VHA policy, notify Office of Research Oversight (ORO), Office for Human Research Protections (OHRP), and FDA, of any adverse event that is both an unexpected and a serious experience for research subjects or others in a research study, any serious or continuing noncompliance with regulations or requirements of the IRB, and any suspension or termination of IRB approval for research. Other federal agencies will be notified of these incidents in accordance with VHA policies and the advice of ORO. NOTE: notification of sponsor shall be the investigator’s responsibility.
6. Monitoring the informed consent process when the IRB determines it to be appropriate
7. Evaluating conducting of protocols and IRB activities
8. Ensuring that initial and continuing education requirements for the IRB Chair, IRB members, and IRB alternate members are met

The IRB shall have the authority to evaluate the effectiveness of recurring procedures to assure that written procedures are followed, to review charts for compliance with written procedures and regulations contained in the VHA Handbook 1200.5, and to monitor the informed consent process and the

performance of the research under relevant regulations and policies. The IRB may also consider results of audits conducted by other entities, both external and within the institution. The information obtained on these audits shall be communicated to the R&D Committee.

0800 The Investigator

The "Principal Investigator" (PI) is the individual under whose immediate direction research is conducted and reported or, in the event of an investigation conducted by a team of individuals, the responsible leader of that team. The "Responsible Investigator" must be a VA staff member who serves as the PI in the eyes of the VA. The Responsible Investigator is the person to whom the VA turns in cases of VA specific adverse reactions, clinical emergencies related to research, financial issues, etc. In some cases, the Responsible Investigator might not be identical to the PI. This is a division of responsibility negotiated by the investigators themselves.

0801 Investigator Responsibilities

1. Investigators shall ensure that they and their research staff involved with a human subject protocol follow good clinical practice in the conduct of clinical research and comply with all applicable federal regulations.
2. Investigators shall obtain appropriate education and be certified to conduct research involving human subjects by a program that meets all VA requirements.
3. The investigator shall see that members of the research team receive all required training.
4. Investigators shall develop a research plan that is scientifically valid, minimizes risk to subjects, and contains a description of the data and safety monitoring plan (DSMP) when appropriate.
5. Investigators whose research involves human subjects shall be responsible for ensuring that informed consent is obtained from each subject or the subject's legally authorized representative, unless the requirement has been waived by the IRB.
6. Investigators are required to prepare and maintain adequate and accurate case histories for each subject. The case history for each individual must document that informed consent was obtained prior to participation in the study when informed consent is a requirement of the approved protocol.
7. Investigators shall ensure that adverse events, as defined by the DSMP in the protocol, and all reports of the Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), are reported in accordance with the monitoring plan approved by the IRB and as defined in FDA regulations or other applicable federal regulations. Serious Adverse Events (SAE), or Unexpected Adverse Events (UAE), shall be reported to the IRB and the R&D Committee. The VA Central Office, as well as other federal agencies or sponsors, shall also be notified as required. [NOTE: See 0603 5a for more information about

reporting of AE's]

8. Investigators shall submit for approval all amendments to or modifications of the research proposal, including the consent form, to the IRB and R&D Committee prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.
9. The investigator shall be responsible for obtaining initial and continuing R&D Committee and IRB review and approval, and for submitting to the R&D Committee and the IRB requests for modifications to the protocol.
10. The investigator shall know the date of continuing review and that the project shall be automatically suspended when continuing review does not occur on schedule. No research activities, except those necessary to ensure the safety of the subjects, can occur if either R&D Committee or IRB approval has lapsed.
11. The investigator shall also notify (in writing) the pharmacy of approvals prior to initiation of the protocol.
12. The investigator shall be responsible for ensuring that copies of all amendments, advertisements, informed consent documents, and R&D Committee and IRB protocol approvals and other documents, are in the investigator's study files.

Investigators who end their relationship with the Cincinnati VA must submit final reports to the R&D Committee for all VA projects for which they are responsible. Investigators must complete the necessary clearance forms to ensure proper and appropriate disposition of all research matters, including laboratory chemicals, equipment, experimental drugs dispensed through Pharmacy Service, and research employees appointed specifically for the investigators' program. If an investigator leaves the Cincinnati VA without submitting a final report, the designee will administratively terminate the study.

When a protocol changes from one principal investigator (PI) to another (as a result of resignation or retirement, for example), the change must be approved by the R&D Committee. In that event, care shall be exercised to assure that any identifiable subject information remains confidential and becomes the responsibility of the new PI.

The Investigator may bring forward to the Chair of the R&D Committee and/or the IRB Committee any concerns or suggestions regarding the Human Research Protection Program including but not limited to the review process of either committee. Such reports, suggestions, complaints or compliments are made with complete protection of the reporting individual from any discrimination or reprisal.

0802 Investigator Eligibility for VA Research Support

1. An investigator may apply to VA Central Office (VACO; Washington, D.C.) for research funds if s/he has at least 5/8^{ths} salaried appointment at the VA, or has been deemed "eligible" by the Eligibility Committee of VACO.

2. An investigator may apply to the Cincinnati VA Research Service for other support (laboratory space, access to clinical materials, etc.) if s/he has a VA appointment of any kind (1/8th or more of salary, WOC status, etc.), and if s/he makes a significant contribution to the VA mission as defined by the Medical Center Director, Chief of Staff, ACOS/R, and/or R&D Committee.

0900 Off-Site and Multiple Site Research

VHA policy mandates that VA-funded research be performed in laboratory or office space within the VA Hospital, related clinics, or VA-approved space when possible. This mandate applies to research involving human subjects and all other types of research. If needed, an off-site waiver must be approved by the Chief Research and Development Officer (CRADO) prior to initiation of the research. A waiver shall be requested even if only a portion of the work will be performed off-site ("a partial off-site waiver").

If human subject research is being conducted at the Cincinnati VA as well as at other sites, each institution is responsible for safeguarding subjects' rights and following appropriate procedures at all sites involved.

1000 Reporting to the Office of Research Oversight (ORO)

The Office of Research Oversight (ORO) reports to the Under Secretary for Health on all matters affecting the integrity and ethical conduct of VA research. ORO is responsible for investigating allegations of research improprieties and research misconduct.

The Cincinnati VA Medical Center, through the Medical Center Director is responsible for reporting information relevant to oversight concerns to the Mid-Atlantic Regional Office of ORO (Washington, DC). If it is necessary to provide ORO with such information, the VISN 10 Director shall be simultaneously notified and sent a copy of the same information sent to ORO (unless the sensitivity or confidentiality necessitate a more limited distribution of the information).

Cincinnati VA must provide ORO with written information concerning the following events:

1. Findings of serious or continuing noncompliance with the regulations for the protection of human subjects, the requirements of the IRB, Federal regulations, or VHA policies.
2. All research-related adverse events (AEs) and imminent threats of AEs that result in:
    a. An IRB taking action(s) that materially alter the substance and meaning of a protocol, the informed consent form or process, or investigator status, or
    b. An unexpected death of a research subject.

3. Suspension or termination of IRB approval.
4. Suspension/termination of Research Safety Subcommittee approval.
5. Any serious injury to personnel requiring hospitalization or leading to serious complications or death.
6. Any exposure, release, loss, or theft of select agents or toxins, or other serious incident reporting and reevaluation of the safety or emergency plan.
7. Any citation or reportable findings from an Office of Research and Development (ORD) site visit or audit, from the National Institutes of Health (NIH) on research involving recombinant DNA, from the Center for Disease Control and Prevention (CDC) or the USDA concerning hazardous materials, from the Occupational Safety and Health Administration (OSHA), from the Nuclear Regulatory Commission (NRC), or from the VA National Health Physics Program.
8. Any Type 1 contingency following a Joint Commission on Accreditation of Health Care Organizations (JCAHO) site visit related to research safety.

The following must be reported directly to ORO Central Office:

1. Any change in status of the Federal Wide Assurance (FWA; see definition) or the IRBs (e.g. changes in institutional officials, IRB chair/membership.
2. All initiations of inquiries and investigations of research misconduct (i.e., fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting results).
3. Copies of inquiry and investigation reports concerning research misconduct.
4. All adjudications (both finding of research misconduct and findings of no research misconduct).

1100 Gifts and Gratuities

The Veterans Affairs Medical Center's Policy on Gifts and Gratuities is defined in Cincinnati Department of Veterans Affairs Medical Center, Cincinnati, Ohio MEMORANDUM NO 00-74, Titled: Commercial Vendors, Dated July 20, 2004 Section I "Gifts and Gratuities". This policy is as follows:

1) In general, employees and on-site trainees may not solicit or accept any type of gratuity from a commercial vendor including gifts, favors, entertainment, transportation, lodging, snacks or meals, services or training (other than training as part of a contract). The acceptance of pens, notepads or other trivial items is discouraged; any such acceptance must comply with 5 CFR 2635.204 (a).

2) On occasion, employees may accept certain items of value (e.g. off-site training that includes a meal) only under specific conditions, such as when offered to the larger medical/academic community. This is permissible under 5 CFR 2635.201-205 (value not to exceed $20 per source per occurrence and $50 per source per year, with no active solicitation). Questions concerning the acceptability of items of value should be addressed to the Office of Regional Counsel.

3) Distribution of journal reprints or other informational items to employees or trainees is permitted. However, informational items intended for patient or family education must be approved by Education Service before they are distributed.

1200 Conflict of Interest (COI) Management

Real or potential COIs may affect the real or perceived quality and scientific objectivity of research and the treatment of research participants. Financial and non-financial COIs will be considered, when applicable, by the R&D committee during protocol reviews.

A financial COI is any financial arrangement, or financial situation, that affects, or is perceived to affect, the design, review, conduct, results, or reporting of research activities or findings. The appearance of such a conflict from the point of view of a disinterested party represents a potential COI. Real or potential COIs shall be identified, and procedures for managing, mitigating or eliminating them shall be followed.

Financial interest is defined as anything of monetary value including, but not limited to: salary; payments for services; equity interests; intellectual property rights; and service as an officer, director or other fiduciary role for a financially interested company.

The VA requires that, for each proposed study, full disclosure shall be made of all financial and employment relationships between an investigator or an involved member of a study team, his/her spouse or domestic partner, and his/her dependent children, and the sponsor of a project or any entity with a potential financial interest in the outcome or conduct of the research. This disclosure shall be made as part of the initial research project application process to both the VA R&D Committee and the IRB. Any subsequent financial conflict arising after initial application shall also be reported. These reports shall be reviewed by a COI Administrator, who will identify steps to manage the COI for the IRB, the R&D Committee, and the investigator.

1. Research proposals submitted to VA R&D Committee for review must contain a Conflict of Interest Disclosure Statement. Proposals submitted without the required statements appended shall not be reviewed. Investigators (principal investigator, co-principal investigator, or other) shall report all possible COIs which might relate to the management of research projects or contracts. The committee review shall include discussion of oversight, approval, advising, recommending, or initiating actions on research related projects.

2. In addition to the VA requirements, the University of Cincinnati Conflict of Interest (COI) Committee will review potential Conflict of Interest and make recommendations based upon establishment of Conflict of Interest. Recommendations will be forwarded to the IRB as applicable. The UC COI Committee will review disclosures and provide guidance for managing, reducing, or eliminating actual or apparent conflicts of interest.

Members of the IRB and/or R&D Committee who themselves have a COI must recuse themselves from review of proposals for which the conflict exists. Recusal means that the member leaves the room during both the final committee deliberation and the vote.

The VA COI Administrator shall report to the R&D Committee regarding the material, including all actions concerning COI taken by the IRB and determine whether the proposed project could reasonably appear to be directly and significantly affected by the related financial interest of the investigator(s). A direct effect occurs when:

1. Project results would be directly relevant to the development, manufacturing or improvement of the products or services of an organization in which the investigator or research participant has a financial interest
2. The organization in which the investigator or research participant has a financial interest is a proposed subcontractor or participant in the project
3. There is a relationship between the project sponsor and the investigator or research participant outside the project that has the potential to affect performance in the project

The R&D Committee may approve the IRB's actions concerning COIs, or add other stipulations or changes, but may not disallow any of the IRB's stipulations or required changes. The R&D Committee shall also be responsible for issues involving COI for studies not involving human subjects. For these studies the committee shall determine what actions should be taken by the institution or the investigator to manage, reduce or eliminate the COI.

Possible remedies for managing or mitigating a conflict include:

1. Investigator severs relationships creating the conflict
2. Investigator divests significant financial interests
3. Investigator discloses relationship with sponsor on all publications, in the consent form provided to human subjects, and in other appropriate public forums
4. Investigator separates research from consulting, etc., providing an acceptable detailed written plan for achieving this
5. Investigator substitutes someone else to serve as project PI and is appropriately distanced from the conduct of the research.

When a significant financial COI exists and cannot be eliminated, the consent form must contain a discussion of the financial arrangement, how the conflict of interest is being managed and the additional protections that have been put in place. The COI Administrator will maintain records of all financial disclosures and all actions taken by the medical center, with respect to each COI (as long as protocol records are maintained). The inability to resolve significant conflicts of interest will be reported to the Medical Center Director, through the R&D committee.
For CVAMC Conflict of Interest Guidance, please refer to Medical Center Memorandum 151-016 "Conflict of Interest Relating to all Research Personnel"

1201 Failure to Comply with Conflict of Interest Policy

If an investigator fails to comply with the COI policy or with corrective actions requested by the IRB and/or the R&D Committee, the failure to comply will be reported to the VA Medical Center Director. Any failure to comply with conflict of interest policy and/or corrective actions pertaining to a specific conflict of interest may result in other conditions or restrictions that would be consistent with applicable policies, regulations, and laws.

These conditions or restrictions may include:

1. Termination of the research protocol;
2. Removal of the investigator from the research protocol team; or
3. Revocation of the privilege to conduct research at the Cincinnati VA Medical Center.

The Public Health Service, the Food and Drug Administration, or other applicable entities may also sanction the investigator, depending on the seriousness of the non-compliance and the determination of the research sponsor and responsible agency.

1300 Research Team Training

Key personnel who are involved the design and conduct of in human subjects research (i.e., anyone viewing the data collected from humans, even if those data are coded to protect personal identifiers) must receive appropriate training in ethical principles and accepted practices by which research involving human subjects should be conducted. This includes all investigators (Principal, Co-Principal, and Sub- Principal), research coordinators and research assistants involved in human studies research, all members of the Research Service Office, and voting members of the R&D Committee, and all voting VA representatives on the UC IRB. This training shall include completion of educational courses (this may be a web-based course) Good Clinical Practices (GCP) and Human Subject Protection, Ethics, and the VA HIPAA Privacy Training.

Training must include:

1. Good Clinical Practice and Human Subject Protection training
2. VA HIPAA Privacy Training
3. Ethics

This training must be updated annually (based on the fiscal year Oct 1 – Sept 30) and documented to the Research Service. If these training modules are not completed by September 30th (every year), penalties will occur. It is the principal investigator's responsibility to see that all members of the team receive the required training.

Additional mandatory courses may be required based upon the location of the study and the scope of practice for the study for an individual.

If the research involves components other than human studies, some affiliated research team members may be exempt from the above training requirement, these exempted members might include:

a. those involved in the animal studies arm of a human study,
b. consultants providing advice only on proposed methods
c. team members using only cultured cell lines, etc.

All training must be completed by all research team members prior to approval of a new protocol by the R&D Committee. Research team training will be reviewed annually at the submission of a new protocol or continuing review to confirm compliance. Annual continuation will be approved only upon completion of all training requirements by all team members involved in the research.

1400 Protocol Submission

Research proposals that involve the use of human subjects, medical records or databases, or human tissue, shall be submitted to both the R&D Committee and the UC IRB for their approval prior to any initiation of the study. In the protocol that is being submitted, research investigators shall make provision for the adequate protection of the rights and welfare of prospective research subjects and ensure that pertinent laws and regulations are observed.

1401 Submission to the R&D Committee

Investigators shall submit to the R&D Committee:

1. A copy of:
    a. Request to Review Research Proposal form (a federal form)
    b. Conflict of Interest Forms
    c. VA Application for Initial Review (a local form, see section 1202)
    d. Investigational Drug Information Record (VA form 10-9012)
    e. Informed consent form using VA form 10-1086
    f. Proposed budget
    g. Intellectual Property Agreement Acknowledgement Form
    h. Abstract (<500 words) submitted on both 3.5 diskette and in hard copy
    i. HIPAA Authorization form and/or Waiver of Authorization
    j. Pharmacy Impact Form
    k. Laboratory Impact Form
    l. Statement of Work (SOW) for electronic captures of data by IRM

2. A copy of:
    a. All material submitted to the IRB, including copies of the informed

consent documents
   b. The sponsor's study protocol
   c. Any investigator's drug or device brochure that is part of the study package
   d. IND/INDE FDA Letter

3. An Investigator Data Sheet (a federal form) and a *curricula vitae* (CV) [if this proposal is the first research proposal submitted by the investigator to the VA R&D Committee]
4. The R&D Committee may request one copy of the full application to outside funding agencies (i.e. grant proposals).

NOTE: It is the investigator's responsibility to be aware of changes in submission requirements; Research Service will amend the Cincinnati VA Research Website (http://www.cincinnati.research.med.va.gov) as necessary.

1402 <u>Information to be Included in an Application to the VA R&D Committee:</u>

1. Title of the study
2. Names of Responsible investigator(s) and other staff involved in study
3. VA employment status, Scope of Work, of responsible investigator(s) and other staff (Investigators submitting their first application to the R&D Committee should append a CV to that application)

   NOTE: Every person involved with the study who has contact with VA subjects, their tissues, or their records must have all of their academic degrees and licenses verified by the VA Research Service. Physicians' credentials will have been "verified" by VetPro, so they need not duplicate this verification. Each person involved with a study, other than the principal investigator, must complete a Scope of Work form that describes his or her role in the research. Training requirements are discussed in sections 1100, and 1101.
4. Study design, including:
   a. Purpose of the study (≈ 1 ¶)
   b. Summary description of program (≈ 1 ¶)
   c. Specific aim(s) (≈ 1/2 page)
   d. Background (≤1 page)
   e. Methods and procedures (≤ 5 pages)
   f. References
   g. Previous work by applicant (≈ 2 pages)
5. Sponsor of the study/funding sources
6. Supporting statements by service chiefs and collaborator(s)
7. Future plans and impact of research on the VA Hospital
8. Details of issues concerning the participation of human subjects that shall include (NOTE: this section may be part of, or replaced by, the IRB application itself):

a. Subject inclusion/exclusion criteria
b. Justification for use of any special/vulnerable subject populations
c. Provisions for managing serious adverse reactions
d. Circumstances surrounding consent procedures including: setting, subject autonomy concerns, language difficulties, cultural differences, educational capabilities, and vulnerable populations
e. Procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators and document storage
f. Compensation to subjects for their participation and payment terms;
g. Any compensation for injured research subjects
h. Provisions for confidentiality and the protection of a subject's privacy
i. Extra costs to subjects for their participation in the study
j. Other issues are detailed within the IRB application, e.g., benefits to society, study design (including statistical methodology), risk/benefit analysis, and details on the consent procedures.

NOTE: All staff involved in VA research must have a VA appointment of some kind, either VA salaried or Without Compensation (WOC).

1403 Submission to the IRB

In addition to the above submission material to the R&D Committee, investigators shall also submit to the IRB (details for IRB submission may change, investigators should call the IRB main office at (513) 558-5259 prior to making a submission): or view the IRB website @ www.researchcompliance.uc.edu

1500 Review Process for Initial Submissions to the R&D Committee

Once the initial review application is found to be complete:

1. It shall be placed on the R&D Committee agenda for the following meeting. Primary reviewers will be assigned for each committee
2. All members of the committee will receive a copy of the protocol
3. Primary reviewers also receive a copy of the Investigator's Drug Brochure (IDB) or Investigational Device Exemption (IDE) specifications, if applicable
4. Reviewers shall present the protocols and relevant information at their respective meetings. Submissions may be simultaneous to both the R&D & IRB committees.
5. The R&D Committee shall endorse (recommend for approval), request specific modifications (acceptable pending), defer, or disapprove the protocol and forward its recommendation to the IRB, or other subcommittee as appropriate
6. The response from the R&D Committee will be forwarded to the Principal Investigator
7. No final approvals will be granted until both the R&D Committee and the IRB have reviewed and endorsed the protocol as approvable

1600 Documentation of R&D Approval

Approval of a protocol is determined based upon:

1. Final approval letters from all subcommittees (IRB, IACUC, SRS and Radiation Safety Committee)
2. Completion of all required training for PI and all study personnel.
3. Final approval letter from the R&D Committee

The duration of the approval shall be guided by the durations of approval granted by the tolerant subcommittees, (example – IRB)

1700 The IRB Review Process

For UC IRB policies and procedures regarding the IRB Review Process, to include exempt research and continuing review of research please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259.

1800 The R&D Committee Review Process

1801 R&D Committee Responses

For research proposals submitted for review and approval, the R&D Committee may vote for the following actions, with specific clarification of the action to be provided to the investigator (the action will be reported to the PI in a notification memo shortly after the meeting):

1. Full Approval – All requirements have been met and the research can proceed
2. Acceptable pending… –The notification memo will specify what is required for final approval. Once made, modifications shall be reviewed administratively (or by specific reviewers as requested by the R&D Committee. A letter of full approval will be signed by the R&D chairperson.
3. Deferred – A proposal may be deferred if there are major concerns that must be resolved before the R&D Committee will reconsider the proposal for approval. A deferred proposal must be reviewed again by the fully convened Committee. The materials, information, modifications, or conditions necessary for reconsideration by the R&D Committee will be stipulated in the notification memo. A proposal may be set aside without review or discussion due to lack of a quorum, missing information, or other reasons that may not relate specifically to the proposal.
4. Disapproved – The proposal may be disapproved and not allowed to be conducted at the VHA. The reasons may relate to such issues as scientific design, ethical issues regarding subject protection, feasibility due to lack of VA Medical Center resources, impact on patients, safety concerns, etc.

The Committee will note items submitted to it for informational purposes only.

1801.1 R&D Committee Approval Period and Dates of Approval

The R&D Committee cannot approve a protocol for a period longer, or a date beyond, that granted by the IRB or other relevant subcommittee.

The R&D approval date is the date at which the fully convened committee or a reviewer acting on behalf of the full committee, voted to approve the protocol. The R&D approval date is not the same as the IRB approval date, which determines when IRB continuing review will take place.

1801.2 Communication of R&D Committee Findings and Actions

All formal communications of the R&D Committee shall be in writing. Reports of R&D actions shall be given to investigators following review of proposal material (initial review, continuing review, etc.). These shall indicate findings, stipulations, requests for additional information, and/or final actions. The chair or a designee of the chair shall sign notification memos. Other official communications shall also be done in writing to the ACOS/R, Chief of Staff, Hospital Director, VA National Headquarters or other federal agencies as necessary.

1802 Appeal of an R&D Committee Decision

An investigator may appeal any decision by the R&D Committee. If a study is disapproved, the proposal may be resubmitted with a cover letter detailing how the concerns and/or objections to the previous submission have been addressed or providing additional clarifications for areas that may have been not correctly reviewed due to lack of details. For other actions such as suspension or termination of a study, an appeal letter may be sent to the R&D Committee. Since the R&D Committee cannot override the disapproval action for a research activity made by any of its subcommittees, the objections and concerns of the subcommittee(s) must be addressed before the R&D Committee will take any final action.

1803 R&D Continuing Review

The R&D Committee shall review all projects at least once a year to assess scientific progress and continued appropriateness of the research to the overall VA mission. The date of continuing review may correspond to the continuing review date of the IRB.

1900 Protocol Changes

1901 Submitting Protocol Changes

Investigators shall submit any changes, amendments, or modifications to an active protocol to the R&D Committee. The R&D Committee must review and approve any changes prior to initiating any changes.

Examples of items that need to be submitted as Changes include:

1. Protocol amendments and changes
2. Revisions to consent forms
3. New or revised recruitment materials (e.g. newspaper, radio, or flyer advertisements; web site information)
4. Investigator drug brochure (IDB) amendments and changes
5. Revisions to HIPAA Privacy Rule forms
6. Change in investigator
7. Any other changes that might alter the risk, potential benefits, or rights of the subjects

If the investigator submits a change of protocol and decides to not incorporate the changes in the research, it is important to notify the R&D Committee in a timely way.

1902 Expedited Protocol Changes

Minor changes that will not alter the risk, potential benefits, or rights of the subjects may be submitted as Expedited Changes. Examples of these include:

1. Minor changes to Advertising materials
2. Consent form changes that do not affect the Risk/Benefit ratio
3. The addition of, or changes to, a subject diary card
4. The addition of, or changes to, a subject diary questionnaire
5. New recruitment materials
6. Other minor changes that are not medical in nature

2000 Documentation and Record Keeping

Records are the property and the responsibility of the CVAMC Research Service. The medical center shall designate where the records will be maintained under lock and key.

Non-redacted IRB minutes relevant to the VA shall be submitted to the R&D Committee and maintained by the Research Service. The R&D Committee shall review, and where appropriate, act upon the IRB minutes.

2001 Record Retention

Required records shall be retained for a minimum of 5 years after the completion of the study and in accordance with VHA's Records Control Schedule, applicable FDA and DHHS regulations, or as required by outside sponsors.

All records shall be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA and other authorized entities at reasonable times and in a reasonable manner.

2002 Research Service Records and Documentation

2002.1 R&D Committee Administrative Records

R&D Committee records maintained by the Research Service shall include the following categories:

1. Written operating procedures
2. R&D Committee membership roster showing qualifications of the members (including CVs) and any conflict of interest (COI) statements
3. Copies of correspondence relating to membership appointments
4. Training records (reports or certificates of human studies protection training, other related training)
5. R&D Committee correspondence (other than protocol related documents)
6. Minutes of R&D convened meetings

2002.2 Records Relating to Investigators and Research Projects

Information relative to the qualifications and VA appointment status of each principal investigator shall be maintained by the Research Service (e.g. CVs and documentation of training).

For each approved project, the R&D administrative files shall contain the following items:

1. All materials submitted by the Principal Investigator (PI) for initial review
2. All materials and correspondence from the PI to the Research Service related to protocol amendments, adverse events, continuing review, and termination of study
3. All approved informed consent documents
4. All study related correspondence sent or received by the R&D Committee or any R&D subcommittee
5. Any other related documentation regarding the study received by the Research Service

2002.3 Access to/Retention of R&D Committee Records

All research records shall be kept confidential and secure in locked filing cabinets in the Research Administration Offices. Normal access is limited to the ACOS/R, the Administrative Officer(s) for Research, research administrative staff, chairs of the R&D Committee or its subcommittees, authorized VA representatives, officials of federal or state regulatory agencies and appropriate accreditation organizations. All other access to R&D records is limited to those who have legitimate need, as determined by the VA Hospital Director, the ACOS/Research (or designee) and/or VA Central Office (VACO).

Research records relating to a study shall be retained for at least 5 years after approval for a study is terminated. The minimum requirement may be exceeded in accordance to applicable VA, FDA and DHHS regulations, or as required by outside sponsors of the study. The R&D records relating to an investigator shall be retained for at least 5 years after the PI leaves the Cincinnati VA Medical Center. All closed files will be stored at Iron Mountain Records Management. Stored boxes will be marked with date of destruction. Iron Mountain will confirm with the RCO and/or AO of Research prior to on-site destruction.

2003 IRB Records and Documentation

For UC IRB policies and procedures regarding IRB records and documentation please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259.

2004 Investigator Records and Documentation

Investigators should maintain records in a way that assures the confidentiality and privacy of individually identifiable subject data, except when required by law or released with the permission of the subject. Subjects have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and that the confidentiality of private information will be preserved. The more sensitive the research material, the greater care required in obtaining, handling, and storing data.

To protect subject confidentiality, the following guidelines are applicable:

1. Limit recording of personal information to that which is essential to the research.
2. Store personally identifiable data securely and limit access to the principal investigator and authorized staff; subject records should be stored in a locked file cabinet or office.
3. Code data as early as possible in the research process, and plan for the ultimate disposition of the code linking the data to individual subjects.

4. Apply for federal Certificates of Confidentiality in situations for which certificates are reasonable and available.
5. Investigators should keep copies of all information submitted to and received from the IRB. IRB correspondence should be maintained in an orderly fashion.
6. The investigator must keep a copy of the informed consent signed by each subject enrolled in a research study, if applicable.
7. Records should be maintained for at least 5 (five) years after the study has closed.
8. Location of the records of the closed studies shall be noted in the final letter to the R&D Committee.

2100 The Use of Investigational Drugs in Human Subjects Research

An investigational new drug is a new chemical compound under clinical investigation that has not been released by the FDA for general use, and which is not approved for marketing. An approved drug that is being studied for an unapproved or new use, or a new route of administration, may also be considered an investigational drug and be subject to VA investigational drug policies, and/or the assigning of an Investigational New Drug (IND) number.

Use of investigational new drugs shall be conducted according to FDA and VA regulations that in brief state:

1. The use of drugs in research shall be carried out in a responsible manner. The storage and security procedures for drugs used in research shall follow all federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations.
2. An investigational drug for clinical research use is may need an IND application filed with the FDA. An IND application goes into effect 30 days after the FDA receives the application, unless the FDA disapproves the application or approves it sooner than 30 days.
3. The PI is responsible for informing the Pharmacy Service that R&D Committee and IRB approval has been obtained. The PI will provide Pharmacy Service with the IRB and R&D approval letters, the Investigational Drug Information Record (VA Form 10-9012)), or superseding forms, a copy of the approved VA informed consent form, the protocol, and the Investigator's Drug Brochure (IDB). To document each subject's consent to participate in the study, the PI will supply Pharmacy Service with a copy of each subjects signed informed consent statement prior to dispensing the first prescription or drug dose. The research pharmacy shall maintain a file of individual consent forms for each person who receives an investigational drug.
4. During the clinical investigation of a drug before the drug is released, if it is needed for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or therapy is available and in the treatment of patients not participating in clinical trials,

permission for its use must be directly granted by the FDA if adequate time is available. The FDA permits such use only if:

a. For a serious disease condition: there must be sufficient evidence of safety and effectiveness to support such use.
b. For immediately life-threatening disease: the available scientific evidence, taken as a whole, must provide a reasonable basis for concluding that the drug:
   – May be effective for its intended use in its intended patient population; or
   – Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

5. FDA regulations provide for situations where clinicians cannot receive timely approval from the FDA itself for emergencies. This includes waiver of consent as well as waiver of FDA approval. There are two specific situations:
   a. When the investigator, and a physician who is not otherwise participating in the study, certify in writing that a human subject is confronted by a life-threatening situation necessitating the use of the drug, and where a legally effective informed consent cannot be obtained from the subject, and where time is not sufficient to obtain consent from the subject's legal representative AND where there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject, or
   b. If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject and time is not sufficient to obtain the independent determination described in “a” in advance of using the drug

   NOTE: The use of an investigational drug under such circumstances (a or b) must be reported to the IRB within 5 working days
6. Should a patient seeking medical treatment at the Cincinnati VA be found to be a subject in a Non-VA approved research protocol utilizing investigational drug, the pharmacist , <u>prior to dispensing the investigational drug</u>, must:
   a. Contact the Research Principal Investigator or designee directly to determine continued eligibility to receive investigational drug.
   b. Secure a copy of the protocol, IRB letter of approval, investigational drug brochure and a copy of the current signed informed consent (of the patient).
   c. Alert both the R&D chairperson and the ACOS/Research of the situation in writing within 24 hours of the situation.
   d. Make an entry of this situation into the medical record electronic file.

   The Research Administration must send a letter of acknowledgement signed by both the R&D chair and the ACOS/Research, within one business day , of the situation to the pharmacist and copied to the Medical Center Chief of Staff.

2101 Storage and Procurement of Investigational Drugs

Investigational drugs used in human subjects studies at the Cincinnati VA that are not on the Hospital Formulary are available for use only within the context of the study. Use within a study does not guarantee that the drug will be available for that patient after the study is over. Continued use of a non-formulary drug after a study is completed is subject to non-formulary use criteria. The principal investigator shall coordinate the handling of the investigational drug(s) with the Research Pharmacist. All investigational drugs are to be kept in the pharmacy and dispensed only by prescription or physicians order. Prescriptions for study drugs will only be honored from designated physicians who are listed on the VA form 10-9012. Investigational drugs shall be properly labeled and stored in the pharmacy and will only be used under direct supervision of the principal investigator or designee.

2200 The Use of Investigational Devices in Human Subjects Research

Use of an investigational device in a clinical trial to obtain safety and efficacy data shall be conducted according to FDA's Investigational Device Exemption (IDE) regulations, 21 CFR 812, other applicable FDA regulations, and applicable VHA regulations:

For UC IRB policies and procedures regarding the use of investigational devices in human subjects research, please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259.

1. Significant risk device studies shall be conducted in accordance with the full IDE requirements. Pursuant to these regulations, an investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation. The investigator shall obtain approvals from the IRB and R&D Committee.
2. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of the IDE regulations.
3. Once a determination is made that the device does not present a significant risk, studies may commence immediately following IRB and R&D Committee approval if there are no changes required by either committee.
4. The PI is responsible for compliance with all applicable FDA regulations.
5. **For further VA guidance please refer to Medical Center Memorandum 151-13, “Use of Investigational Devices”.**

2201 Storage and Procurement of Investigational Devices

If an investigational device is being used for human studies, the PI must complete and submit an investigational device control sheet, containing information on the storage, security and dispensing of the device, to the R&D committee prior to its approval of the study. It is the responsibility of the PI to ensure that the investigation is conducted according to the study protocol and applicable FDA regulations for the control of devices under investigation.

All devices received for study will be stored in a locked environment, under secure control with limited access. This environment may be within an area controlled by the investigator, or pharmacy facilities may be used. The device may be used only with, or dispensed to, subjects who have undergone an appropriate consent process. Depending on the nature of the device (either used directly by the investigator, or provided to the subject for individual use), there shall be properly supervised use, or proper instructions for the use of the device. In addition, a log should be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

2300 Recruitment and Selection of Subjects

All participants in human subjects research under VA-purview shall be recruited in an equitable, non-coercive manner. As part of the recruitment process, subjects shall be fully informed about the risks and benefits their participation entails. Both the VA R&D Committee and the IRB must approve all recruitment materials including informed consent forms, strategy for identifying and recruiting subjects, and advertising.

2301 Content of Recruitment Materials

Recruitment materials can include newspaper advertisements, flyers, TV or radio spots, letters or emails to patients, and other forms of advertisement. Advertisements designed to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. The following items may be included:

1. The general nature of the experiment
2. The name, address, and contact information of the clinical investigator and/or research coordinator and facility
3. The condition under study and/or the purpose of the research
4. In summary form, the criteria that will be used to determine eligibility for the study
5. A brief list of participation benefits, if any (e.g., a no-cost health examination)
6. The time or other commitment required of the subjects
7. The location of the research and the person or office to contact for further information

2302 Special Case Recruitment Issues

2302.1 Non-English speaking subjects: Consent documents must be written in the language that is most easily understood by the subject. A potential subject's inability to read, or to read English, is not an appropriate basis for exclusion from most research. For investigators proposing to use non-English language consent documents, procedures should be developed to ensure the translation of the document from English to the second language. The IRB shall review all non-English consent forms and recruitment materials. The IRB may request certification of the accuracy of the translation.

2302.2 Students/Trainees: If students, residents or fellows are serving as research subjects, participation must be voluntary and free of coercion. Investigators need to be sensitive to any possibility of coercion or the appearance of coercion (due to a desire to appear particularly cooperative or highly motivated, or because participation in research is a course requirement).

When students or trainees are to be involved in research, the following guidelines are applicable:

a. personal solicitations by the investigator shall be avoided,
b. advertisements for students/trainees should be broad based (i.e., investigators should not recruit primarily from their own section), and
c. the informed consent document should address potential coercion.

2302.3 Employees: Hospital employees, such as office staff, lab technicians, and post-doctoral fellows, are similar to students in that they are vulnerable to pressures, even if not intended, to appear cooperative and supportive of their supervisor's work. Investigators shall avoid recruiting employees from the investigator's own lab or office unless approval for such recruitment is received from the IRB.

2303 Participation of Non-Veterans as Research Subjects

Most regulations pertaining to the participation of veterans as research subjects shall apply also to non-veteran subjects enrolled in VA approved research.

In case a research-related medical need arises, the following considerations apply:

1. If the subject is eligible for medical care as a veteran, all necessary and appropriate care will be provided by the VA.
2. If the subject is not eligible for medical care as a veteran, humanitarian emergency care will be provided, and further treatment will be made available on a case by case basis as determined by the VA.

A VA medical record may be initiated for non-veterans enrolled in clinical studies conducted at the Cincinnati VA. Subjects may be enrolled in the hospital computerized record system.

For subjects enrolled in survey or non-interventional research studies, original consent documents for non-veterans will be maintained in the investigator's file. However, for these subjects, a medical record need not be initiated.

2304 Payment of Research Subjects

VA policy prohibits paying human subjects to participate in research when the research is an integral part of a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care. Payment may be permitted, with approval of the IRB and the R&D Committee, in the following circumstances:

1. No direct subject benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice at the UW is to pay subjects in this situation.
2. Others being paid. In multi-institutional studies, when human subjects at a collaborating in non-VA institution, such as the UC, are to be paid for the same participation in the same study.
3. Comparative situations. In other comparable situations in which, in the opinion of the IRB and R&D Committee, payment of subjects is appropriate.
4. Transportation expenses. When transportation expenses are incurred by the subject, that would not be incurred in the normal course of receiving treatment, and that are not reimbursed by any other mechanism.

Prospective investigators who wish to pay research subjects shall in their proposal:

1. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject.
2. State the terms of the subject participation agreement, the amount of payment and the time frame for payment in the informed consent form.
3. Show that subject payments do not constitute (or appear to constitute) undue pressure, influence, or coercion on the prospective research subjects to volunteer for or continue to participate in the research study.

The IRB and R&D Committee shall review all proposals for payment of subjects to assure conformity with VA policies. This review will include consideration of the schedule of payments to avoid any coercion that might result from withholding all or most payment until the end of a long trial.

The Research Service is responsible for ensuring that the approved payment to subjects is made from a VA approved funding source for research activities.

2400 Subject Privacy and HIPAA Regulations

The new federal Privacy Rule, part of the federal Health Insurance Portability and Accounting Act, or HIPAA, went into effect on April 14, 2003. The Veteran's Health Administration (VHA) is committed to conducting research in compliance with the HIPAA Privacy Rule. All investigators or study team members using or disclosing protected health information, who are involved with a Cincinnati VA study, shall comply with the Privacy Rule. The rule provides protections for the confidentiality of health information used in clinical practice, research, and the operations of health care facilities, in order to ensure that health information confidentiality risks are minimized. The Privacy Rule supplements Common Rule regulations related to the protection of the privacy of human subjects in research.

All individuals who are involved in human studies research shall receive HIPAA Privacy Rule training.

1. Learning Management System available at:
   □
2. Employee Education System available at:
   http://www.ees.aac.va.gov

HIPAA Privacy Rule requirements related to submission of human subject protocols include:

1. All individuals who will use or disclose protected health information must obtain certification that they have completed required training related to HIPAA Privacy Rule research regulations.
2. Investigators need to provide additional details within R&D applications related to the protection of human subject privacy.
3. Researchers will be required to create and use an authorization form to obtain a subject's written permission to use or disclose their protected health information (PHI). Alternatively, researchers may submit an application for a Waiver of Authorization, Partial Waiver of Authorization, or Altered Authorization, for circumstances under which obtaining written authorization is impractical and presents minimal risk to subjects' privacy.

The HIPAA Privacy Rule protects "individually identifiable health information," referred to as protected health information (PHI). PHI includes information that:

1. Is created or received by a covered entity, which includes a health care provider, and
2. Relates to the past, present, or future physical or mental health, or condition of the individual, or
3. Relates to payment for the individual's health care, or
4. Relates to the provision of health care in the past, present, or future, and
5. Identifies an individual, or could be used for identifying an individual.

The IRB subcommittee reviewing the protocol will serve as the Privacy Board which

will evaluate compliance with the HIPAA Privacy Rule. To comply with the Privacy Rule as it applies to the use or disclosure of PHI for research purposes, investigators shall complete one or more of the following actions/documentations:

1. Written authorization specifically for the use and disclosure of PHI for research purposes involving human subjects
2. Waiver of authorization approved by the IRB
3. Use of de-identified information or limited datasets
4. Signing of Preparatory to Research Certifications
5. Database registration

An investigator using protected health information (PHI) before beginning research activities under an approved protocol or exemption (such as surveying a patient list to learn if the project is feasible, or to learn which patients are suitable) shall make representations about the use of PHI by signing a "Preparatory to Research Certification". Investigators who are database custodians may not use their own databases preparatory to research activities unless they have made this certification.

An investigator using PHI in a research protocol, after screening and selecting subjects shall:

1. Obtain a signed and valid research authorization from each subject/participant, or
2. Obtain a waiver of authorization from the IRB, or
3. Use one of the following sets of individual health information as permitted by the Privacy Rule:
    a. A limited data set after signing a data use agreement with an outside data custodian, or after signing a data use certification for use of data for an internal data custodian.
    b. De-identified information, to which the Privacy Rule does not apply.

2401 <u>De-identification of Individual Health Information</u>

To comply with HIPAA privacy regulations, one of the following two methods shall be followed to de-identify subject protected health information (PHI):

1. either remove the specific identifiers listed in the Privacy Rule and determine there is no other information that may identify the individual, or
2. obtain an opinion from a qualified statistical expert that the risk of identifying an individual is very small under the circumstances; the methods and justification for the opinion should be documented

The identifiers are:

a. Names
b. Geographic subdivisions where a subject lives smaller than a State
c. Elements of dates (except year) related to an individual (including dates of admission, discharge, birth, death and, for individuals over 89 years old, the year of birth must not be used)
d. Telephone numbers

e. FAX numbers
f. Electronic mail addresses
g. Social Security numbers
h. Medical record numbers
i. Health plan beneficiary numbers
j. Account numbers
k. Certificate/license numbers
l. Vehicle identifiers and serial numbers including license plates
m. Device identifiers and serial numbers
n. Web URLs
o. Internet protocol addresses
p. Biometric identifiers (including finger and voice prints)
q. Full face photos and comparable images
r. Any unique identifying number, characteristic or code

2500 Informed Consent of Research Subjects

The investigator shall be responsible for obtaining and documenting legally effective informed consent using the current consent forms which have been approved for the research by both the IRB and the VA R&D Committee, and for ensuring that no human subjects are involved in the research prior to obtaining consent. For making copies, use only consent forms that have been stamped and approved by the IRB. VA consent form 10-1086 shall be used for all VA funded research**.** Informed consent must be obtained prior to any research-related screening procedures, where the screening involves direct contact with prospective subjects or patients.

If any changes are made to the protocol throughout the life of a study, consent forms must be changed to reflect applicable changes. If consent forms are altered, subjects must provide a new consent with updated (approved and stamped) informed consent forms.

Signed consent forms must be filed as follows:

1. Original: In the subject's case history
2. Copies:
   - One to the subject, or their legally authorized representative
   - One in the investigator's research file (maintained for 5 years)
   - One in the VA Pharmacy (if investigational drugs are involved)

A subject has a clear and free choice to accept the invitation to participate or to refuse without prejudice or penalty. If subjects are students, patients, or employees, they must be informed that nonparticipation or withdrawal from the study will not affect their grade, treatment, care, employment status, etc.

2501 Obtaining Informed Consent

Legally effective informed consent of a subject, or the subject's legally authorized representative, shall be obtained prior to an investigator involving a human being as a subject in research. If someone other than the investigator conducts the interview and obtains consent, the investigator should delegate this responsibility, and the person so delegated should have receive appropriate training to perform this activity. The person so delegated shall be knowledgeable about the research to be conducted and the consenting process, and shall be able to answer questions about the study. In all cases, the most recent IRB and R&D Committee approved consent form shall be used.

1. An investigator must seek subject consent to participate in a research study under circumstances that:
    a. provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate, and
    b. minimize the possibility of coercion or undue influence.
2. No informed consent, whether oral or written, will include any exculpatory language through which the subject or the subject's representative will be made to waive or appear to waive any of the subject's legal rights, or which releases or appears to release the investigator, the sponsor, the VA Hospital, or its agents from liability for negligence.

All consent forms must contain the Basic Elements for Informed Consent, as defined in 38 CFR 16, these are listed in Appendix 1.a. Additional Elements for Informed Consent (Appendix 1.b) shall be included in consent forms when relevant. The IRB or the R&D Committee may request additional elements.

NOTE: The IRB may require translations of consent forms when non-English or limited-English speakers are enrolled in the study.

2502 Documentation of Informed Consent

Except as described below, informed consent shall be documented by the use of a written consent form approved by the IRB and the R&D Committee and signed and dated by the subject or the subject's legally authorized representative. The consent form shall also be signed and dated by a witness whose role is to witness the subject's, or the subject's legally authorized representative's, signature. The investigator must sign the consent form, along with the person obtaining consent if that person is other than the investigator. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the subject's signature, the same person should serve both capacities and a note to that effect shall be placed under the witness's signature line.

1. The VA Form 10-1086, VA Research Consent Form, or an electronic version

of VA Form 10-1086 shall be used as the template for the consent form for all VA funded research.

2. The consent form shall be the most recent R&D Committee and IRB-approved consent form. The IRB documents its approval by the use of a stamp on the first page of the consent form that indicates the date of its most recent approval of the form. The IRB shall maintain a copy of the approved form in its records.
3. The original signed consent form will be filed either in the subject's case history (a.k.a., the “chart”, “hospital record”, “treatment record”, or “clinical record”), or in the investigator’s records.
4. A copy of the informed consent (signed, if feasible) shall be provided to the subject or the subject's legal representative.
5. The medical record, electronic or paper, will be flagged to indicate the subject's participation in the study and the source of more information on the study. The patient's medical record shall NOT be flagged if:
    a. The subject's participation in the study involves only the use of a questionnaire or the use of previously collected biological specimens, or
    b. The identification of the patient as a subject in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

The consent form shall be the following:

1. Written Consent Document. The (paper or electronic version), Research Consent Form, shall follow the template version found on the IRB website. The consent form shall embody the elements required as described here and in 38 CFR 16.116 (see Appendices 1a, 1b). In addition, it shall contain any additional elements as required by the IRB. The consent form may be read to the subject or the subject's authorized representative. The investigator shall ensure that the subject (or representative) is given adequate opportunity to read the form and ask questions before signing it.

A progress note documenting the informed consent progress shall be placed in the subject's medical record (unless this places the subject as risk in an otherwise minimal risk study). At a minimum, the progress note shall include the name of the study, a brief description of the study, the person consenting the subject, a statement that the subject or the subject's representative was capable of understanding the consent process, a statement that the study was explained to the subject, and a statement that the subject was given the opportunity to ask questions.

An entry shall also be placed in the progress note when the human subject is actually entered into the study and when the human subject's participation is terminated. Consent and entry notes can be combined when both occur at the

same visit. When research is initiated on the same day as informed consent is obtained, the time of consent shall be documented in addition to the date.

2503 Alternative Forms of Consent

Informed consent shall be obtained from every potential subject in a clinical trial who is a physically and mentally able adult. The term “assent” (agreement) is used when referring to children, minors, or to adults with compromised abilities to provide informed consent. In some cases, the IRB and R&D Committees may grant a waiver to the researchers to omit or alter some elements of informed consent.

1. **Children or Minors** – VA investigators while on official duty or at the VA or VA-approved off-site facilities shall not conduct research involving children or minors less than 18 years of age, unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable federal regulations (see 45 CFR Part 46, Subpart D 46.401 – 46.409).

2504 Research Involving Human Subjects with Surrogate Consent

Under appropriate conditions, investigators may need to obtain consent from the legally authorized representative of a subject (surrogate consent) in order to conduct essential research on problems that are unique to persons who are incompetent or who have an impaired decision making capacity (e.g., a study of treatment options for comatose persons).

Such consent shall be obtained from one of the following:

1. A health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) or similar document
2. A court-appointed guardian of the person
3. From next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse; adult child (18 years or older); parent; adult sibling (18 years or age or older); grandparent; or adult grandchild (18 years of age or older)

    Such consent shall be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note (see Appendix 1.c for details on such determination).

Before an incompetent person or persons with impaired decision-making capacity may be considered for participation in any VA research, the IRB shall evaluate whether the proposed research meets all of the requirements for using mentally ill subjects or subjects with impaired decision making capacity as human subjects in research (see section 2503.1 of this document: “Rules Governing Research

When Subjects Have Impaired Decision Making Capacity").

2505 Waiver of Informed Consent

NOTE: It is important to differentiate between waiver of the need to obtain informed consent and waiver of documentation of informed consent.

In general, informed consent shall be obtained from all subjects. However, under certain circumstances, altering or omitting elements of written consent documents may be approved by the IRB. The requests for a waiver of consent or documentation of consent must be fully justified by the researcher when submitting an application. **Please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259 for additional information on the waiver of informed consent.**

2506 Waiver of Documentation of Informed Consent

In some cases, informed consent cannot be waived, but the requirement for documentation of informed consent may be waived. The IRB may require the investigator to provide subjects with a written statement regarding the research.

Please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259 for additional information on the waiver of documentation of informed consent.

A waiver of informed consent documentation does not imply waiver of the investigator's responsibility to obtain informed consent from subjects upon the terms required by the IRB.

2506.1 FDA Exceptions to Requirement for Documentation of Consent

In research studies involving FDA regulated investigational products, the requirements for informed consent shall not be waived. However, the requirement for documentation of informed consent (i.e., a signed written consent form) may be waived under certain specific conditions.

According to FDA regulations, documentation of informed consent shall be required except as follows:

1. If the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, or
2. FDA requirements for planned emergency research are met (NOTE: this exception is not allowed for VA studies)

2600 Risk-Benefit Analysis for Human Subjects Research

2601 Risks

The IRB shall assess the risks vs. anticipated benefits of research as one of its primary functions. In addition, once risks and benefits have been assessed, the IRB is responsible for ensuring that the risks of study participation are minimized and reasonable in relation to the anticipated benefits of study participation.

For definitions of risk, minimal risk and anticipated benefit used by the IRB please refer to their website at http://researchcompliance.uc.edu

Before submitting a protocol, investigators shall clearly distinguish procedures that are standard of care from those which are conducted solely for research purposes in the protocol and informed consent form.

2602 Categories of Risk

2602.1 Physical Risk

Some biomedical research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation may result in physical harm to subjects. For all research with the potential to cause physical harm, investigators need to think through all risk possibilities so that they can be resolved quickly and minimize the harm to subjects. Investigators need to address procedures to minimize physical risk to the greatest extent possible.

2602.2 Psychological Risk

Some research has the potential to cause undesired changes in thought processes and emotion including episodes of depression, confusion, hallucination resulting from drugs, feelings of stress, guilt and loss of self-esteem. Investigators need to address procedures to minimize psychological risk to subjects.

2602.3 Social and Economic Risk

Some research involves the handling of sensitive information that may result in injury to subjects through a breach in confidentiality. These breaches may result in embarrassment within a subject's business or social group, loss of employment, or criminal prosecution. The IRB shall be especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior and illegal activities. Research may also pose direct economic risk to study subjects (e.g., billed procedures, transportation cost, loss of wages). Investigators should minimize economic costs to subjects.

2602.4 Minimal Risk

Assignment of research for expedited review, approval of waiver of consent, and the conduct of research involving vulnerable research populations may be dependent upon whether the research places subjects at minimal risk or greater than minimal risk (see section 2401 for definition of Minimal Risk).

2603 Benefits

2603.1 Benefits to the Individual

Research may provide subjects with treatment, diagnosis or examination for an illness or abnormal condition. In these cases, the research involves evaluations that may benefit the subjects by improving their condition or provide a better understanding of their disorder. Investigators shall detail these potential benefits in their initial submission, and in the informed consent form, while not overstating these benefits. Investigators should fully describe any benefits to the subject or to others that may reasonably be expected from the research.

2603.2 Benefits to Society

Although research may not always provide a benefit to society, researchers are encouraged to design research projects so that information, in the form of generalizable knowledge, can contribute to societal benefit whenever possible. Investigators should detail these potential benefits for the IRB in their application, and for the subjects in the informed consent form, while not overstating these benefits. Research which does not provide benefit to individuals should provide a reasonable likelihood of benefits for society.

2700 Special Consideration for Vulnerable Subjects

Additional protections shall be provided to vulnerable populations participating in VA research.

NOTE: VA regulations may be more restrictive than DHHS regulations and guidance. When this occurs, the VA/VHA regulations shall be followed.

Definitions:

1. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (the Health Sciences IRB Office considers children as those under 18 years of age).
2. Delivery means complete separation of the fetus from the woman by expulsion, extraction, or any other means.
3. Fetus is the product of conception from the time of implantation to delivery.
    a. Viable fetus is now termed a “viable neonate”
    b. Nonviable fetus is a fetus *ex utero* that, although living, is not able to survive to the point of independently maintaining heartbeat and respiration. NOTE: In 45 CFR 46 Subpart B, this definition is used as the

definition of a non-viable neonate.

c. Dead fetus is a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

4. *In vitro* fertilization is any fertilization of human ova that occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.
5. Neonate means newborn.
    a. Viable neonate means being able, after delivery, to survive to the point of being independently maintaining heartbeat and respiration (given the benefit of available medical therapy).
    b. Non-viable neonate means the same as non-viable fetus.
6. Pregnancy is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.
7. Prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained in such institutions pending arraignment, trial, or sentencing.

Vulnerable populations as listed in the Federal regulations include:

1. Pregnant women and fetuses
2. Prisoners
3. Mentally ill and those with impaired decision making capacity
4. Children
5. Educationally or economically disadvantaged persons

2701 <u>Pregnant Women and Fetuses as Vulnerable Populations</u>

Research involving a fetus, *in-utero* or *ex-utero* (including human fetal tissue) shall not be conducted by VA investigators while on official duty or at VA facilities or approved off-site facilities.

VA investigators while on official duty or at VA facilities or approved off-site facilities shall not conduct research related to *in vitro* fertilization.

For research involving the participation of pregnant women as research subjects, the IRB and R&D Committee must:

1. Determine that the proposed research meets the following requirements:
    a. Appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing potential risks to pregnant women and fetuses is provided
    b. The purpose of the activity is to address the health needs of mothers or

fetuses with conditions like the condition of the subject, for example, toxemia of pregnancy or urinary tract infection. The risk to the fetus must be minimal, and, in all cases, there is the least possible risk for achieving the objectives of the activity

c. Individuals engaged in the research activity have no part in: any decisions regarding timing, method, or procedures used to terminate pregnancy; determining the viability of the fetus at the time of termination of the pregnancy; introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy

2. Determine that no inducements, monetary or otherwise, are offered to terminate pregnancy for purposes of research activity.
3. Determine that no pregnant woman is involved as a subject unless she is legally competent and has given informed consent after having been fully informed regarding possible impact on the fetus. NOTE: The father must also give informed consent unless the purpose of the activity is to meet the mother's health needs; he is not reasonably available; his identity/whereabouts are unknown; or the pregnancy resulted from rape.

[NOTE: protections for these populations are described in DHHS regulations 45CFR46 Subpart B. These are not described here due to VA restrictions]

2702 Prisoners as a Vulnerable Population in Research

Research involving prisoners shall not be conducted by VA investigators while on official duty or at VA approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (CRADO).

[NOTE: protections for these populations are described in DHHS regulations 45CFR46 Subpart C. These are not described here due to VA restrictions]

2703 Mentally Ill Persons or Those Persons with Impaired Decision Making Capacity as a Vulnerable Population in Research

Research involving subjects who are mentally ill or subjects with impaired decision-making capacity warrants special attention. Research involving these populations frequently presents greater than minimal risk, may not offer direct medical benefit to the subject, and may include a research design that calls for washout, placebo or symptom provocation. In addition, these populations are considered to be vulnerable to coercion.

2703.1 Rules Governing Research When Subjects Have Impaired Decision Making Capacity

The IRB membership will include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a

person or a representative of an advocacy group for that population.

Please refer to the UC IRB website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259 for additional information on rules governing research when subjects have impaired decision making capacity.

2704 Children as a Vulnerable Population in Research

Research involving children shall not be conducted by VA investigators while on official duty or at the VA or approved off-site facilities, unless a waiver has been granted by the Chief Research and Development Officer (CRADO).

[NOTE: protections for these populations are described in DHHS regulations 45CFR46 Subpart D. These are not described here due to VA restrictions]

2705 Economically or Educationally Disadvantaged Subjects

Federal regulations require that when some or all of the subjects are likely to be vulnerable to coercion or undue influence due to being economically or educationally disadvantaged, additional safeguards must be included in the study to protect the rights and welfare of these subjects. (see also section 2402.3)

Such safeguards include, but are not limited to:

1. Ensuring that compensation is commensurate with risk, discomfort, or inconvenience involved
2. Avoiding recruiting in settings where the voluntary nature of participation might be compromised without taking appropriate precautions to ensure that consent is voluntary

2800 Research Using/Storing Human Biological Material and Genetic Research

Research involving biological material, including genetic material, that can be linked, directly or indirectly by a code, to personal information concerning the source of the material is subject to federal regulations and therefore shall be reviewed by both the R&D Committee and the IRB.
Research using unlinked samples may require review to ensure that the process by which the material is rendered unidentifiable is appropriate and secure. Research using only unidentified samples may be exempt from IRB review.

Research using human genetic material or genetic testing poses special concerns and always requires full review by both the R&D Committee and IRB. A project involving human biological materials may be reviewed through the expedited review process provided that the project meets the criteria for such review.
For all research protocol related biological material:

1. Whenever possible, all subject identifiers shall be removed from specimens
2. The link between specimens and the donors shall remain with the investigator sending the samples
3. The VA shall have approval authority over any future uses of banked specimens
4. If an investigator uses a non-VA tissue bank (defined in VHA Directive 200-043 as an issue repository or storage facility), and it ceases operations, the VA must receive assurances that all specimens obtained from VA subjects are destroyed.

NOTE: It is prohibited for VA investigator to participate in non-VA tissue banks without Office of Research and Development (ORD) approval

When informed consent is being obtained in studies involving tissue banking, consent forms must clearly state:

1. If the specimen will be used for future research, and allow the subject choice of how the specimen will be used (e.g., any research, research only by the PI or affiliated researchers, genetic analysis, research related to a specific area)
2. If research results of reuse of the specimen will be conveyed to the subject
3. If the subject will be re-contacted after the original study is completed
4. If the subject requests, the specimen and all links to the clinical data will be destroyed
5. If the (stored) specimens are sent to a non-VA institution for testing/use as defined in the protocol, once the specific analyses are performed, the institution must certify the destruction of the specimens in writing

2900 Using VA Records for Research and Development

VA personnel are bound by all legal and ethical requirements to protect the rights of human subjects, including the confidentiality of information that can be identified with a person. These requirements include HIPAA regulations (see sections 2200, 2201).

VA personnel may obtain and use medical, technical, and administrative records from this and other VA facilities or VA databases for R&D purposes (in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information). In addition, the R&D Committee and the Director of the facility from which records are requested shall approve the release of those records.
Persons not employed by VA can be given access to medical and other VA records for R&D purposes only within the legal restrictions imposed by such laws as the Privacy Act of 1974 and 38 U.S.C. Requests for such use shall be submitted to the CRADO in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act ordinarily requires a response within 10 (ten) working days. VA guidelines and policy must be followed when making such requests to allow for a timely reply. This does not apply to individuals having access for the purpose of monitoring the research. Obtaining and using the records shall be in

compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information.

All use of records must fulfill HIPAA Privacy Act requirements, in addition their use may be subject to IRB and R&D Committee review if it is for research. It is the responsibility of the investigator to contact the IRB to determine if the proposed record use is considered research.

3000 Adverse Events Reporting and Documentation

The principal investigator (PI) is responsible for accurate and timely reporting to the ACOS/R, the R&D Committee, and the IRB, any serious adverse event (SAE) unexpected adverse event (UAE) or other unanticipated problems that involve risks to subjects. In addition, the VA research pharmacist should receive copies of all serious and unexpected adverse events involving investigational drugs.

In general, SAEs are events that are life threatening, or involve hospitalization or extension of hospitalization. UAEs are events that that are not identified in the protocol and/or consent form. Non-physical events, such as severe emotional distress, loss of job due to a research-related breach of confidentiality, or other psychological, social, or economic event, also may be considered an SAE or a UAE. It is important that investigators are cognizant of sponsor requirements (e.g. what constitutes an SAE, how and when to report adverse events).

Serious adverse events (as defined in the protocol) other than local deaths shall be reported to the R&D committee within 7 (seven) business days of the investigator becoming aware of the event if they meet the following criteria:

1. They are unexpected (including occurring at a higher than expected rate)
2. They are possibly related to study treatment

Deaths of subjects on VA research studies at the VA Hospital must be reported to the IRB and VA R&D Committee within 5 (five) business days.

If the event is an "unanticipated" adverse effect of an investigational device, the PI is required to report to the R&D Committee as soon as possible but not later than 10 (ten) working days after the PI first learns of the event. All SAE's are reviewed by the ACOS Research for the R&D Committee **and he/she will determine whether these events were unanticipated problems involving risks to participants or others.**

The prompt reporting of unauthorized use, loss or disclosure of individually identifiable patient information must occur to the VAMC Privacy Officer and RCO.

Violations of the VAMC information security requirements must also be

promptly reported to the appropriate VHA Information Security Officer and the RCO.

Investigators must also report any instances of serious or continuing problems, or non-compliance to the VA Research Service and the IRB in a timely fashion. NOTE: The Research Service and the IRB have the authority to suspend or terminate protocols that are found to be non-compliant, or which have been associated with unexpected serious harm to subjects.

If the study has a Data Monitoring Committee (DMC) or Data Safety and Monitoring Board (DSMB), a copy of the most recent DMC/DSMB report shall also be submitted to the IRB as part of the continuing review.

For additional information regarding adverse event reporting (and continuing review) to the UC IRB please refer to their website at http://researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259.

Investigators shall also follow all additional sponsor specified adverse event reporting requirements as described in the study protocol.

3100 Safety Monitoring Plan

All multi-center studies utilizing an IND are required to have a Safety Monitoring Plan. The plan is to be submitted with the protocol application for review and approval by both the R&D Committee and the IRB. The plan may vary depending on the potential risks, complexity and nature of the study.

The Safety Monitoring Plan shall ensure the safety of participants in on-going clinical research studies and the validity and integrity of research data collection. The Safety Monitoring Plan must include a mechanism for reporting adverse events to both the IRB and to the R&D Committee, and when required to ORO, ORD and other Federal agencies.

The Safety Monitoring Plan needs to address the nature of the safety monitoring and who will be conducting that monitoring. It may be reasonable for a single individual to perform the monitoring in a small trial with minimal/low risk, whereas a local independent or external Data Safety Monitoring Board may be required for more complex/high risk trials (e.g., multiple clinical sites, interventions are particularly high-risk, or vulnerable populations are included), or when required by NIH or FDA. If a DSM Board is used, all events (AE, UE, SAE) shall be reported to the DSM Board and a summary of the board's findings shall be reported to the R&D Committee, the IRB, and other entities as required.

Key elements to be incorporated in a Safety Monitoring Plan:

1. Assessment of risks and monitoring level to be employed
2. Safety contact: state who is responsible for data and safety monitoring
3. Safety monitoring: describe who will conduct the monitoring and how often will it occur
4. A detailed plan for the informed consent process (e.g. how and when subjects will be consented; what will be included in the consent form)
5. A description of the data collection process
6. Adverse events monitoring:
    a. Description of anticipated adverse events
    b. AE grading method
    c. Reporting of unanticipated adverse events
    d. Plans for periodic reporting
    e. Impact on termination of subjects from the study and study closure

Please refer to the UC IRB website at http://researchcompliance.uc.edu for additional information on safety monitoring plans, or call the UC IRB office at (513) 558-5259.

3200 Complaints and Allegations of Noncompliance

All research subjects, investigators, research staff, and others involved with research are encouraged to ask questions about the rights of research subjects or to voice concerns or complaints concerning research. Research subjects and others may address their complaints or inquiries about a research project by contacting the University of Cincinnati Medical Institutional Review Board at 513-558-5259. This contact information shall be given to subjects as part of the informed consent process, and the number will be included on Informed Consent Forms.

NOTE: Informed consent forms may also refer the subjects to the Cincinnati VA Research Compliance Officer at (513) 475-6414.

The RCO will:

1. Ensuring a response to each question, concern or complaint
2. Investigating complaints and allegations
3. Taking remedial action for noncompliance with VA HRPP and Research Service policies
4. Identifying individuals responsible for responding to questions, concerns or complaints regarding an individual's rights as a research subject. These personnel will include the Principal Investigator and pertinent study staff.

For matters that require formal inquiry, the Human Research Protection Oversight Committee shall designate an appropriate individual to conduct an initial review, as appropriate to the nature of the complaint, non-compliance issue, or impropriety. **If the complaint is determined to be an issue of non-compliance, follow the**

procedures outlined in CVAMC Medical Center Memorandum 151-019, Non-Compliance in Research. If the complaint it determined to be an issue of an unanticipated problem, it will be deferred to the IRB policies and procedures on Unanticipated Problems in Research which can be found at www.researchcompliance.uc.edu or by calling the UC IRB office at (513) 558-5259. During this review, every effort will be exercised to maintain the confidentiality of all parties involved. The ACOS/R and other appropriate parties will be notified of the incident and that an inquiry has begun. Findings and recommendations from this review will be forwarded to the ACOS and the AO for Research.

The ACOS/R, with the assistance of other program officials as necessary (AO/R, RCO, etc.) will evaluate the facts gathered and take appropriate action. Dependent upon the nature of the event or circumstances, certain actions may occur:

1. Further inquiry may be initiated
2. Administrative action may be taken
3. Details and recommendations forwarded to the appropriate committees (R&D, IRB, Biosafety, etc.) for consideration and action
4. Details and recommendations forwarded to the appropriate Service Chief for action
5. Details and recommendations forwarded to the Chief of Staff and/or the Medical Center Director for action
6. Copy of details and recommendations forwarded to the IRB Chairperson and UC Research Compliance Officer
7. Other actions as deemed appropriate

3300 Suspension of Protocol

Research may be suspended for a variety of reasons including failure of timely review. If continuing review does not occur within the timeframe set by the IRB, the research is automatically suspended, and the IRB will notify the R&D Committee Chairperson and the RCO of the suspense. The IRB or Research Compliance Officer will notify the PI of the suspension. For suspended research, enrollment of new subjects cannot occur and continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interest of individual subjects to do so.

Once notified of the suspension, the PI shall respond to both the IRB and/or R&D their findings in writing. The sponsoring agency, private sponsor, ORD, ORO or other Federal agencies shall be informed by the VA or by the IRB when appropriate. Once a project is suspended, IRB and R&D Committee review and reapproval must occur prior to re-initiation of the research.

3400 Conclusion or Termination of Protocol

At the conclusion or termination of a human subjects research study, a final report shall be submitted by the principal investigator to the IRB and the R&D. The report must include the findings, whether positive or negative of the study and other information relating to the appropriate closure of the study, including the reason for closure.

Once a study is closed, there shall be reasonable ongoing procedures in place as appropriate and practicable, to protect subject confidentiality and to provide feedback of relevant emerging information to former subjects.

The biomedical or other intervention study is considered closed when:

1. Subjects are no longer being recruited or enrolled
2. All active participation of the subjects has ended, and all study interventions have been stopped
3. The investigator is no longer accessing private identifiable information
4. No further contact with participants/records/specimens is anticipated
5. All review of records and/or specimens has been halted
6. Data are not being actively collected in any form, nor are existing data being analyzed other than for statistical reporting

If an investigator leaves the Cincinnati VA without formally terminating the study or transferring responsibility to another investigator, the ACOS/R will administratively terminate the study.

3500 Publications and Presentations of VA Research

The VA expects its contributions to medical and scientific research to receive due credit, and places the burden of responsibility on its research investigators to comply with this policy. The VA and its employees have a responsibility to ensure that the Department receives proper credit for VA-supported research in articles, presentations, interviews, and other forms in which the results of that research are publicized. Therefore, all publications arising from VA research shall acknowledge support from the VA, whether or not the investigator has a VA Merit Review grant.

Failure to acknowledge VA support or employment may result in discontinuation of current VA R&D funding and/or ineligibility to receive future R&D funding for up to 5 years. In extreme circumstances, it may also result in the revocation of the privilege to conduct research at the VA.

All publications and presentations of VA research results shall contain the following (or equivalent) acknowledgement:

> "This report is based upon work supported (or supported in part) by the Department of Veterans Affairs."

NOTE: This requirement also applies to situations in which the VA provided no direct

research funding, but the research involved the use of other VA resources, e.g., facilities or patients, or investigator's salaries.

Authors of clinical and research manuscripts, abstracts, books, book chapters, and presentations shall acknowledge their VA employment in the by-line, e.g., "Veteran's Affairs Medical Center, Cincinnati, Ohio". When the author also holds a faculty appointment, the academic title and school also may be acknowledged. The VA affiliation shall be listed first when the following conditions apply:

1. The Principal Investigator (PI) has a 5/8ths or more VA appointment, regardless of whether VA is the primary source of research funding
2. Work was funded primarily from VA resources (50 percent or more), either directly or indirectly
3. The research was conducted primarily in VA facilities

Scientists and physicians with VA salaries and/or funding support shall, when presenting their work or discussing it with the news media, make a serious and good-faith effort to obtain appropriate recognition for VA. A serious and good faith effort requires:

1. Securing a verbal agreement that VA will be cited in news reports before participating in a media interview, or
2. Prior to interviews, providing news media with a document on VA letterhead that:
    a. contains the investigator's name, VA title, and Veteran's Affairs Medical Center, Cincinnati, Ohio
    b. explains the importance to the VA of citing the investigator's VA employment in any resulting feature, and
    c. expresses a preference that the investigator's VA title be used when media time or space limitations permit the use of only one professional title.
3. The media's failure to acknowledge VA support despite an investigator's good-faith effort to comply will not jeopardize the investigator's funding.

The publication of research results by firms providing contracted services to VA shall be governed by terms of the contract. The contract terms shall allow for review by the Research Service, and acknowledgement of VA support.

3600 Definitions and Abbreviations

Adverse Event (AE) –any untoward physical or psychological occurrence in a Human Subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article; an AE does not necessarily have to have a casual relationship with the research. NOTE: Adverse events (AE, SAE, UAE) potentially may be physical, psychological, social or economic.

Serious Adverse Event (SAE) – a life threatening experience, hospitalization (if subject not already hospitalized), prolongation of hospitalization (for a subject already hospitalized), persistent or significant disability/ incapacity, congenital anomaly/birth defects, death, or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

Unexpected Adverse Event (UAE) -- any adverse event/reaction, the specificity or severity of which is not consistent with study documentation (including informed consent, investigator brochure, and protocol).

Assent – The agreement to participate in a research study given by a child, or an adult who lacks full decision-making capacity or authority to give legal informed consent.

Assurance – An agreement between an organization and a federal agency that stipulates methods by which the organization will protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally supported research involving human subjects must obtain an Assurance in accordance with 38 CFR 16.103. NOTE: All research conducted under VA auspices is considered to be Federally supported.

Federal-Wide Assurance (FWA) – The agreement between the Cincinnati-VA and OHRP and ORO that stipulates method(s) by which the organization will protect research participants. (66 Fed. Reg. 19139, 19141 (April 13, 2001). This will replaced the MPA as of October 31, 2003.

Multiple Project Assurance (MPA) –The agreement between the Cincinnati-VA, all UC faculty and facilities and OHRP that stipulates the method(s) by which the organization will protect the rights and welfare of research participants. Under OHRP, MPAs will be replaced by FWAs.

Blinded – A study design comparing two or more interventions in which the investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects. Also called a masked study design.

Common Rule – Federal Policy for the Protection of Human Subjects that applies to

All research involving human subjects that are conducted, supported, or otherwise "subject to regulation" by any federal department or agency. The VA's adoption of the Common Rule is codified at 38 CFR 16; the DHHS edition is 45 CFR 46. In January 1991 the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Common Rule. NOTE: DHHS has three additional Subparts in the regulations that are not in 38 CFR 16.

Data and Safety Monitoring Plan – A protocol plan for the review of the integrity, safety and progress of a trial with the purpose of protecting trial participants during the course of study and periodically recommending continuance, modification, or stopping of the study for reasons of efficacy or safety.

Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) – An independent body that is assigned to conduct DSM reviews.

Exempt Research – Exempt research is research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more of certain minimal risk categories (38 CFR 16.101(b)). NOTE: Refer to VHA Handbook 1200.5 for additional information on exempt research. Please also refer to the UC IRB policies and procedures at http:researchcompliance.uc.edu or call the UC IRB office at (513) 558-5259 for additional information on exempt research.

Expedited Review – A review of research involving human subjects by the IRB chair or by a reviewer designated by the chair form among members of the IRB in accordance with requirements set forth in the Common Rule in lieu of review by the full committee.

Good Clinical Practices (GCP) – An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. These regulations apply to the manufacturers, sponsors, clinical investigators, institutional review boards, and the medical device. The primary regulations that govern the conduct of clinical studies are included in the Code of Federal Regulations, Title 21 (21 CFR) and the International Code of Harmonization for Good Clinical Practice (ICH GCP).

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule –The federal Privacy Rule, intended to regulate the creation, use, disclosure, and transfer of health information created or maintained by health care providers. While not intended to regulate the conduct of research, the Privacy Rule does have implications for the use of protected health information in the conduct of research. It contains sections that impose requirements on those involved in research, both individuals and institutions. [HIPAA contains sections other than the Privacy Rule, such as Standards for Electronic Transactions, and Security Standards, which are not currently applicable in this context]

Human Research Protection Program (HRPP) – A comprehensive system to ensure the protection of human subjects participating in research that includes all structural units,

policies, and activities critical to protecting individuals studied in research and that is managed in accordance with these standards and with applicable federal, state and local laws. The HRPP consists of a variety of rules, processes, documents, individuals and committees. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

Human Subject – A living human about whom an investigator conducting research obtains 1) data through intervention or interaction with the individual or 2) identifiable private information (38 CFR 16.102(f)). The Common Rule definition includes investigators, technicians, and others assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled. NOTE: The FDA definition of human subject differs according to the applicable regulation. See 21 CFR 812.3(p), 21 CFR 50.3(g), 312.3(b,) and 56.102(e).

Informed Consent – A voluntary agreement by an individual to participate in research. The individual must have legal and mental competence and the capacity to understand the information transmitted and its implications, after having been informed of the physical, psychological and personal risks and potential benefits entailed by a research protocol. Informed consent is usually demonstrated by signing a consent form, but it may be oral (under specific criteria approved by an IRB). (38 CFR 16.116). Informed consent may also be obtained from a legally authorized representative when the subject does not have the capacity to give informed consent.

Institution – The institution of concern in these SOPs is the Cincinnati, Ohio Veterans Affairs Medical Center (Cincinnati VA) and its satellite facilities including community-based outpatient clinics.

Institutional Official (IO) – The Hospital Director, or IO, is the legally authorized representative of the Cincinnati VA, and as such is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research.

Institutional Review Board (IRB) – A committee comprised of scientific, non-scientific, and non-affiliated members established in accordance with the Common Rule to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB operates and functions in conformance with 21 CFR 56, 45 CFR 46, and 38 CFR 16. Two University of Cincinnati IRBs oversee VA research: the Health Sciences IRB (HS-IRB), and the Health Sciences Minimal Risk IRB (MR-IRB).

Investigational Device – As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3(g).

Investigational Device Exemption (IDE) – An FDA-approval of the application for an "exemption" that permits an un-marketed device to be shipped for the purpose of doing research on the device. NOTE: See 21 CFR 812.1 and 812.2 for scope and applicability. NOTE: An IDE is NOT exempt from IRB review; exemption here only refers to a permit to lawfully ship the device without complying with other requirements of the Food, Drug, and Cosmetic Act that would apply to devices in commercial distribution.

Investigational Drug – A drug or biological product used in a clinical investigation. An investigational drug may be an approved drug that is being studied for a previously unapproved use and/or efficacy.

Investigational New Drug (IND) – A new drug or biological product that is used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes (21 CFR 812.1 312.3(b)). NOTE: The terms "investigational drug" and "investigational new drug" are often used interchangeably.

Investigator – An individual under the direction of the Principal Investigator (PI) who is involved in some or all aspects of the research project, including study design, study conduct, data analysis and interpretation, and preparation of publishable material. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970. The FDA considers investigator and PI to be synonymous.

Principal Investigator (PI)/Responsible Investigator – The "Principal Investigator" is the Individual under whose immediate direction research is conducted and reported or, in the event of an investigation conducted by a team of individuals, the responsible leader of that team. The "Responsible Investigator" must be a VA staff member who serves as the PI in the eyes of the VA. The Responsible Investigator is the person to whom the VA turns in cases of VA specific adverse reactions, clinical emergencies related to research, financial issues, etc. In some cases, the Responsible Investigator might not be identical to the PI. This is a division of responsibility negotiated by the investigators themselves.

Legally Authorized Representative – An individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Monitoring – The act of overseeing the progress of a research study to ensure that the rights and well-being of participants are protected, that the data are accurate, complete and verifiable, and that the conduct of the research is in compliance with the protocol, with applicable regulatory requirements and with standards of the field.

Minimal Risk – When the probability and magnitude of harm or discomfort anticipated in the research is not greater in and of themselves than those ordinarily encountered in the subject's daily life or during the performance of routine physical or psychological examinations or tests (38 CFR 16.102(i); 21 CFR 50.3(k)).

Office for Human Research Protections (OHRP) – A division of the Department of Health and Human Services (DHHS) that monitors human research subjects protections through educational efforts, site visits, and reporting requirements. The OHRP has the authority to suspend research for failure to adhere to the regulations. OHRP replaces the earlier Office for Protection from Research Risks (OPRR).

Office of Research and Development (ORD) – The office within the VA Central Office responsible for the overall policy, planning, coordination, and direction of research activities within Veteran's Health Administration (VHA).

Office of Research Oversight (ORO) – The primary VHA office for advising the Under Secretary for Health on all matters regarding compliance and oversight of research in the protection of human subjects, animal welfare, and research safety. ORO oversees investigations of allegations of research misconduct. ORO replaces the earlier Office of Research Compliance and Assurance (ORCA).

Protocol – A formal plan that includes, at minimum, the objectives, rationale, design, methods and other conditions for the conduct of a research study.

Quorum – A majority of the voting members as listed on the R&D Committee/IRB membership lists. At meetings, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. Requirements for quorum at IRB meetings include other considerations (see section 0602: IRB Composition/Review by Quorum).

Research – The Common Rule defines research as "a systematic investigation including …development, testing and evaluation designed to develop or contribute to generalizable knowledge." Further, as described in the Belmont Report "the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or to contribute to generalizable knowledge... Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective". Research can include any collection of observations intended for presentation to a scientific meeting or for publication in scientific print or electronic medium.

Research Records – Consist of IRB records as well as case histories (also referred to as investigator's research records), or any data gathered for research purposes.

> IRB Records – Include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member.
>
> Case History – The record of all observations and other data pertinent to the investigation on each research subject. Case histories include the case report forms

and supporting data including signed and dated consent forms, any medical records including, but not limited to: progress notes, hospital chart(s), nurses' notes, and investigator's case report forms and supporting data.

Safety Reports – Written reports from sponsors notifying the Food and Drug Administration and all participating investigators of any adverse experience associated with the use of a drug, biologic or device that is both serious and unexpected.

Sponsor – a person or other entity (usually the manufacturer of the drug or device being studied) that initiates but does not actually conduct the investigation.

Test Article – A drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

VA-approved Research – VA-approved research is research that has been approved by the local VA R&D Committee.

Veteran Status – Veteran status is the primary factor in determining a veteran's eligibility to receive VA health care benefits. In general, veteran status is established by active duty service in the military, naval, or air service and a discharge or release from active military service under other than dishonorable conditions.

Vulnerable Subjects – Individuals who lack the capacity to provide informed consent or whose willingness to participate in research may be unduly influenced by others.

Without Compensation (WOC) – Type of VA appointment for a person not salaried by the VA, but who works at the VA in a position other than as a consultant or contractor.

3700 Appendices

Appendix 1: Informed Consent

1A. Basic Elements for Informed Consent

In seeking informed consent, the following types of information must be provided to each subject (combining elements from the Common Rule with VA-specific requirements):

1. Name of the study

2. The name of the Principal Investigator (or VA responsible investigator, if different)

3. A statement that the study involves research

4. An explanation of the purposes of the research and the expected duration of the subject's participation

5. A description of the procedures to be followed

6. Identification of all procedures that are experimental and identification of those that are considered standard of care

7. A description of any reasonably foreseeable risks or discomforts to the subject including, for example, privacy risks (legal, employment and/or social)

8. A description of any benefits to the subject or to others that may reasonably be expected from the research.

9. A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.

10. A statement describing the extent to which confidentiality of records identifying the subject will be maintained [If appropriate, a statement that Federal agencies such as FDA, OHRP, and GAO may have access to the records. If an FDA regulated test article is involved, the FDA suggests that the subject be told that the FDA may choose to inspect research records that include the subject's individual medical records].

11. For research involving more than minimal risk, an explanation as to whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and if so, what they consist of, or where further information may be obtained.

    If the research is a VA approved research project, language regarding "Research Related Injuries", shall be included in the consent form. The VA Research Service

currently recommends the following text:

> "In the event you sustain physical injury as a result of participation in this investigation, if you are eligible for medical care as a veteran, all necessary and appropriate care will be provided. If you are not eligible for medical care as a veteran, humanitarian emergency care will be provided, and further treatment will be made available on a case-by-case basis. You realize you have not released this institution from liability for negligence. Compensation may or may not be payable, in the event of physical injury arising from such research, under applicable federal laws"

This regulation does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances shall be included in the consent form. It is strongly suggested that the investigator make provisions for coverage of such costs in research awards and contracts.

12. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject [at least one contact's name and phone number must be other than that of the investigator or study personnel].

13. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty of loss of benefits to which the subject is otherwise entitled.

14. The VA requires a statement that a veteran-subject will not be required to pay for care received as a subject in a VA research project (with exceptions for category 7 veterans).

1B. Additional Elements of Informed Consent

One or more of the following elements of information shall also be provided to each subject when appropriate:

1. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject, or to embryo or fetus if the subject is or becomes pregnant.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

3. Any additional costs to the subject that may result from participation in the research, other than described in #11 above, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

6. The approximate number of subjects involved in the study.

7. If the investigators believe that the human biological specimens obtained could be part of or lead to the development of a commercially valuable product or if the specimens will be retained after the end of the study, guidance and regulations found in VHA Handbook on Banking of Human Biological Specimens shall be followed.

8. As appropriate, a statement regarding any payment the subject is to receive and how payment will be made.

1C. Determination of Subject Incompetence or Impaired Decision Making Capacity

Determination as to whether a research subject is incompetent or has an impaired decision-making capacity shall be made in accordance with requirements in paragraphs (a-d) below, or as established by a legal determination.

1. The practitioner, in consultation with the chief of service, or chief of staff, may determine after appropriate medical evaluation the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
2. Consultation with a psychiatrist or licensed psychologist shall be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.
3. All disclosures which otherwise would be made to the subject by the investigator shall be made to the subject's surrogate.
4. If feasible, the practitioner shall explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

Appendix 2: Summaries of Ethics and Regulatory Documents

2A. Summary of Common Rule

"The Common Rule for the Protection of Human Subjects in Research" is a Federal regulation that has been adapted by 17 Federal departments and agencies. The Common Rule applies to all federally funded human subject research and defines the standards and processes researchers and research institutions must follow to safeguard human subjects.

As of August 19, 1991, the VA adopted these regulations. The VA's implementation of the Common Rule is incorporated in Title 38 Code of Federal Regulations (CFR) Part 16 (also codified by the Department of Health and Human Services [DHHS] as 45 CFR 46, Subpart A).

The DHHS 45 CFR 46 also contains 3 sections not included in 38 CFR 16:

Subpart B: Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human *In Vitro* Fertilization

Subpart C: Additional DHHS Protections pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research

The Common Rule directs a research institution to assure the federal government that it will provide and enforce protections for human subjects of research conducted under its auspices. These institutional assurances constitute the basic framework within which federal protections are effected. The VA Hospital is responsible for carrying out the specific directives of the Common Rule. Research proposals must be assessed in terms of risks to subjects and potential benefits. The Common Rule's requirements for selecting subjects and obtaining informed consent shall be met.

The Common Rule requires that a research institution such as the VA Hospital, as a condition for receiving federal research support, establish and delegate to an IRB the authority to review, stipulate changes in, approve or disapprove, and oversee human subjects protections for all research conducted at the institution. Details as to the composition of an IRB are included within the Common Rule. An IRB has the authority to suspend the conduct of any research found to entail unexpected or undue risk to subjects or research that does not conform to either the Common Rule or the institution's additional protections.

According to the Common Rule, the informed consent of a competent subject, along with adequate safeguards to protect the interests of a subject who is unable to give consent, is a cornerstone of modern research ethics, reflecting respect for the subject's autonomy and for his or her capacity for choice. Informed consent is an

ongoing process of communication between researchers and the subjects of their research. It is not simply a signed consent form and does not end at the moment a prospective subject agrees to participate in a research project.

The Common Rule lists both required elements that must be included within an informed consent form, as well as additional elements for specific circumstances. In addition, the Common Rule describes the conditions under which an IRB may modify or waive the informed consent requirement in particular research projects.

The Common Rule also defines and describes other aspects of human subject research that affect the protection of said subjects. These aspects include:

1. Exemption Research;
2. Minimal Risk;
3. Expedited Reviews;
4. Multiple Site Research; and
5. Continuing Review.

2B. Common Rule 38 CFR 16: Sections

16.101 To what does this policy apply?
16.102 Definitions.
16.103 Assuring compliance with this policy--research conducted or supported by any Federal Department or Agency.
16.107 IRB membership.
16.108 IRB functions and operations.
16.109 IRB review of research.
16.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
16.111 Criteria for IRB approval of research.
16.112 Review by institution.
16.113 Suspension or termination of IRB approval of research.
16.114 Cooperative research.
16.115 IRB records.
16.116 General requirements for informed consent.
16.117 Documentation of informed consent.
16.118 Applications and proposals lacking definite plans for involvement of human subjects.
16.119 Research undertaken without the intention of involving human subjects.
16.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
16.121 [reserved]
16.122 Use of Federal funds.
16.123 Early termination of research support: Evaluation of applications and proposals.
16.124 Conditions.

2C. Nuremberg Code – Summary

The first international standard for the conduct of research with human subjects The Nuremberg Code, was written in response to the atrocities of WW II. The Nuremberg Code laid the groundwork for future considerations of the ethics of human subjects research. The Code insisted that human rights in research be protected, and that subjects have the authority to protect themselves. It requires that subjects provide informed, voluntary, competent, and understanding consent and retain the right to withdraw from research at any time. Without the right to withdraw, the subject is obligated to the researcher to determine when it is in the subject's interest to end participation. Other provisions of the Code describe the obligation of researchers to protect the welfare of research subjects: the study should be designed to benefit society; research should be conducted in animals prior to human subjects; the researcher should be qualified to conduct the research; assurances should be provided that unnecessary suffering and death of subjects will be avoided; risks will be minimized; and the researcher will stop any study that places a subject at risk of death or injury.

2D. Belmont Report – Summary

The Belmont Report was issued in 1974 by the Department of Health, Education, and Welfare to summarize the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to suggest guidelines which, if followed, would assure that such research is conducted in accordance with those principles. This report outlines a method IRB members can use to determine if the risks to which research subjects would be subjected are justified by the benefits to be gained. According to this method, those doing the review gather and assess information about all aspects of the research, and consider alternatives systematically and in a nonarbitrary way. The aim is to make the assessment process more rigorous, and the communication between the IRB and the investigator less ambiguous and more factual and precise.

The Report articulates three basic ethical principles that guide the conduct of research with human subjects. They are:

1. **Respect for Persons**: Investigators are required to seek voluntary, written informed consent from potential subjects, with explicit assurances of the voluntary nature of their participation in terms that are easy to understand and when they are not under duress. The consent form will include adequate information about the study that will assist subjects in intelligently deciding whether to participate in research. In addition, respect means honoring the privacy of individuals and maintaining their confidentiality. The Report also discusses how such respect relates to potentially vulnerable populations.
2. **Beneficence**: Researchers should maximize the potential benefits to the subjects and minimize the potential risks of harm. If there are any risks

resulting from participation in the research, then there must be benefits, either to the subject, or to humanity or society in general.

3. **Justice**: The principle of justice means that subjects are selected fairly and that the risks and benefits of research are distributed equitably. Investigators should take precautions not to systematically select subjects simply because of the subjects' easy availability, their compromised position, or because of racial, sexual, economic, or cultural biases in society. Investigators should base inclusion and exclusion criteria on those factors that most effectively and soundly address the research problem.

2E. Declaration of Helsinki – Summary

The "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" was drafted and adopted by the World Association in 1964 and has been amended several times, most recently at the World Medical Association conference in October of 2000. The Declaration of Helsinki is a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects.

2F. Good Clinical Practices (GCP) – Summary

The GCP was prepared by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1997) and published by the US Food and Drug Administration (FDA) later that year. GCP was published with the objective of providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities of these jurisdictions. It provides specific guidelines for the conduct of human subject research.

2G. HIPPA Privacy Rule – Summary

The Health Insurance Portability and Accountability Act of 1996 (Public Law 104-191; HIPAA), was enacted to meet the need for national patient record privacy standards as more protected health information (PHI) is stored and transferred electronically. The "Administrative Simplification" aspect of that law required the United States Department of Health and Human Services (DHHS) to develop standards and requirements for maintenance and transmission of health information that identifies individual patients.

These standards, the HIPAA Privacy Rule, are designed to:

1. Improve the efficiency and effectiveness of the healthcare system by standardizing the interchange of electronic data for specified administrative and financial transactions; and
2. Protect the security and confidentiality of electronic health information.

The Privacy rule is mostly concerned with the use and disclosure of protected health information. For this institution, use is considered the sharing, employment, application, utilization, examination or analysis of information within the Cincinnati VA. Disclosure is the release, transfer, provision of access to, or divulging in any manner of information outside the Cincinnati VA.

The requirements outlined by the law and the regulations promulgated by DHHS are far-reaching--all healthcare organizations that maintain or transmit electronic health information must comply. This includes health plans, healthcare clearinghouses, and healthcare providers, from large integrated delivery networks to individual physician offices.

The law provides for significant financial penalties for violations.

HIPAA standards outline specific rights for individuals regarding protected health information and obligations of healthcare providers, health plans, and health care clearinghouses. The privacy regulations grant healthcare consumers a greater level of control over the use and disclosure of personally identifiable health information. In general, healthcare providers including clinical trials investigators, health plans, and clearinghouses are prohibited from using or disclosing health information except as authorized by the patient or specifically permitted by the regulation. The Privacy Rule includes all personally identifiable health information ("protected health information", or PHI), irrespective of form. There is no longer an exclusion for written medical records never transferred to electronic form or oral communications. The regulations are applicable to all health information held or created by the covered entity. This expansion eliminates the anticipated confusion of handling various categories of records differently.

Concerning human subjects research, the HIPAA Privacy Rule builds upon previous Federal protections such as found in the Common Rule by establishing the conditions under which protected health information may be used or disclosed by "covered entities" (such as hospitals, providers, researchers, etc.) for research purposes. Research is defined in the Privacy Rule as, "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." A covered entity may always use or disclose for research purposes health information that has been de-identified. The Privacy Rule also defines the means by which individual subjects will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them held by covered entities. Where research is concerned, the Privacy Rule protects the privacy of individually identifiable health information, while at the same time ensuring that researchers continue to have access to medical information necessary to conduct vital research.

Appendix 3: Categories of Research Appropriate for Expedited Review

NOTE: At the Cincinnati VA Hospital, research that presents minimum risk to subjects is reviewed by the UC IRB. Expedited review at this institution is usually limited to review of changes in previously approved protocols. Expedited review of initial protocols is not currently employed by the HS-IRBs as a regular procedure.

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 38 CFR 16.110.

1. Clinical studies of drug and medical devices that fall into one of these two categories:
    a. Research on drugs for which an investigational new drug application is not required
    b. Research on medical devices for which an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from either:
    a. Healthy, nonpregnant adults who weigh at least 100 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week
    b. Other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week

3. Prospective collection of biological specimens for research purposes by noninvasive means.
   Examples:
    a. Hair and nail clippings in a nondisfiguring manner
    b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
    c. Permanent teeth if routine patient care indicates a need for extraction
    d. Excreta and external secretions (including sweat)
    e. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying dilute citric solution to the tongue
    f. Placenta removed at delivery
    g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor
    h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth

and the process is accomplished in accordance with accepted prophylactic techniques;

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings
j. Sputum collected after saline mist nebulization

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications).
   Examples:
   a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
   b. Weighing or testing sensory acuity
   c. Magnetic resonance imaging
   d. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler flow, and echocardiography
   e. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

8. Continuing review of research previously approved by the convened IRB as follows:
   a. Research in which the enrollment of new subjects is permanently closed; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects
   b. Research in which no subjects have been enrolled and no additional risks have been identified
   c. Research in which the remaining research activities are limited to data analysis

9. Continuing review of research, not conducted under an investigational new drug application or investigation device exemption where 2-8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Appendix 4: Memorandum of Understanding (MOU)

(Please see scanned MOU beginning on next page)

MEMORANDUM OF UNDERSTANDING BETWEEN
CHILLICOTHE VETERANS AFFAIRS MEDICAL CENTER,
CHALMERS P. WYLIE VETERANS OUTPATIENT CLINIC,
CINCINNATI VETERANS AFFAIRS MEDICAL CENTER
AND
UNIVERSITY OF CINCINNATI

CONCERNING THE USE OF THE UNIVERSITY REGISTERED UC IRB
(UC IRB00000180 AND UC IRB00000725)

EFFECTIVE DATE: 10/11/06

PURPOSE:

The Memorandum of Understanding (MOU) sets forth the agreement between Cincinnati Veterans Affairs Medical Center (VAMC) and the University of Cincinnati (UC) concerning the agreed upon arrangements between same for the use of the University's Registered UC IRB(UC IRB0000180 and UC IRB0000725).

GENERAL AGREEMENT:

Both UC and VAMC have FWAs and so agree to abide by all applicable regulations in the conduct of human subjects research at each facility and specifically to the federal regulations as codified in 38 CFR §16 & §17; 45 CFR §46 Subpart A, 21 CFR §50 & §56; other pertinent federal regulations and guidance; and VA policies specifically, but not limited to handbook 1200.5.

THE CINCINNATI VETERANS AFFAIRS MEDICAL CENTER AGREES:

1. To abide by all approved policies and procedures of the UC IRB.

2. To not seek second opinion regarding the UC IRB decision from another IRB.

3. To abide by the decision of the UC IRB to disapprove, suspend or terminate a study.

4. Provide the University of Cincinnati and its authorized agent(s) access to research subject's clinical records and/or case file to UC IRB as required for monitoring research activity and compliance with applicable law.

5. Assure that the Research and Development Committee (R&D) considers the UC IRB review, and provides initial approval prior to the conduct of covered VAMC human subject research.

6. Provide information to the UC IRB about significant issues that come to light during the VA approval process that might affect the conduct of a protocol

through correspondence between the VAMC Research Compliance Officer and the director of the UC IRB. The R&D minutes will be distributed to the UC IRB once signed by the VAMC Medical Center Director.

7. Provide access and training to UC IRB members and staff regarding VA policies and procedures that govern the VA Human Research Protection Program (HRPP) processes and determinations.

8. Maintain current written Standard Operating Procedures and an Investigator Handbook that incorporate procedures for reviewing and approving VA human subject research.

9. Promptly inform the UC IRB of any problems, including complaints, and serious or unanticipated events, encountered in VAMC human subject research in writing according with UC IRB policies and procedures. Notification will be through the VAMC Medical Center Director or designee.

10. To maintain at least two VAMC employees (for a maximum of 3 years) as full voting members at all times on each of the UC IRBs the VAMC has designated to review its human subjects research. One of the two VAMC members shall be qualified as a scientific voting member. A voting VAMC member must be present during the review of VAMC research. The VAMC Research Compliance Officer shall serve as a nonvoting member.

11. To promptly notify the UC IRB of any modifications to the VAMC FWA or changes to the status of the Assurance documents

12. To not enter into collaboration with any Institution that does not have a FWA and will only use the UC IRB as VAMC's IRB of record.

13. To develop and maintain SOPs that detail how compliance monitoring, audits, and reporting to appropriate regulatory authorities will be handled by administrative officials, compliance officer(s), and the UC IRB and its administrators. To promptly provide the results of any external monitoring or audits of research activity, which has been provided to the R&D Committee, to the UC IRB. This includes visits by sponsors and regulatory/compliance bodies.

14. To actively cooperate with the University of Cincinnati in resolving any problems encountered hereunder.

15. To assure that all key VAMC personnel engaged in research meet both VA and UC IRB training requirements and that there is a tracking system of such training.

16. To make available to the University of Cincinnati the required annual VAMC review and evaluation of the UC IRB structure, function and performance as completed by the Research Compliance Officer for the VA Medical Center Director. This annual report will be reviewed and approved at the R&D Committee prior to VA Medical Center Director approval.

17. To facilitate the use of VA Form 10-1086 for all human subject research utilizing the VAMC as a site or VAMC patients as subjects.

18. To assure that research is conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

19. To adhere to requirements of UC regarding reporting of Conflict of Interest for UC IRB members.

20. To maintain accreditation of it's Human Research Protection Program (HRPP).

THE UNIVERSITY OF CINCINNATI AGREES:

1. To provide access to information from the UC IRB database to approved representatives of the VAMC for the purposes of tracking ongoing VA research activity.

2. To develop mutually acceptable policies for monitoring human subjects research. To be involved in the annual review process of the VAMC SOPs and the Investigator Handbook and to allow representation from the VAMC when UC develops, modifies or reviews their own SOPs.

3. To provide training to VAMC staff and investigators as appropriate for compliance with UC HRPP policies and submission procedures as they apply to VAMC submissions.

4. To maintain an UC IRB SOP that incorporates, either by inclusion or reference, VA policies and procedures applicable to reviewing VAMC human subjects research.

5. To promptly inform the VAMC Research Compliance Officer of any issues or complaints associated with VA research. This includes serious/unanticipated adverse event reports observed in VAMC research.

6. To appoint two salaried (at least 5/8th FTEE) VAMC full voting members to each of the UC IRB(s) of record. At least one of the members must have scientific expertise. At least one VAMC member must be present during full board review of VAMC research.

7. To promptly notify the VAMC of any changes to UC's Assurance status.

8. To develop SOPs that detail how compliance monitoring, audits, and reporting to appropriate regulatory authorities will be take place. Reports of these actions shall be forwarded to the VAMC promptly upon completion.

9. To actively cooperate with the VAMC in resolving any problems encountered hereunder.

10. To ensure that all UC IRB members and staff have received the appropriate training as UC IRB members and about applicable VA policy.

11. To require that the VA Form 10-1086, with all required VAMC language, will be used as the informed consent for all VA human subject research.

12. To maintain VAMC human subjects research records at the UC IRB for 5 years following project termination in accordance with VA Policy. Provide the VAMC ready access to these records for review and /or copying. Consult with the VAMC, and transfer such records to the VAMC if requested, before destruction of any records maintained by the UC IRB.

13. To assure that research is conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

14. To advise VAMC of requirements for reporting Conflict of Interest for UC IRB members.

15. To maintain accreditation of it's Human Research Protection Program (HRPP).

BOTH PARTIES AGREE:

1. To the extent there is any conflict between the provisions of this MOU and the terms of any VA rules, policies, or procedures governing the protection of human subjects in research, the provisions of the MOU shall govern.

2. This MOU shall remain in effect until such time as authorized agents of both VAMC and UC mutually agree, in writing, to terminate or modify this agreement.

3. Termination of this agreement will be in an orderly manner so as not to harm subjects or put subjects at risk.

4. Share information regarding researcher Conflict of Interest.

5. Not to disclose any documents or other information received from the other

party and marked "Confidential" unless required to do so by law. The party intending to disclose such confidential information shall provide the other party with notice as soon as reasonably practicable so that the other party may contest such potential use or disclosure.

By signing this agreement the Medical Center Director grants the UC IRB

1. The authority to approve, require modifications to secure approval, and disapprove all research activities overseen and conducted by the organization.
2. The authority to suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that had been associated with unexpected serious harm to participants.
3. the authority to observe, or have a third party observe, the consent process and the conduct of the research.

SIGNATORIES:

Linda Smith
Director
Cincinnati Veterans Affairs Medical Center

10/19/06
Date

~~Fred Hamilton, J.D.~~
~~Associate General Counsel~~
~~University of Cincinnati Medical Center~~

10/23/06
Date

Charles E. Jake IV, Esq.
Assistant General Counsel
Assistant Contracting Officer

Appendix 5: Other Research Resources Available to VA Investigators

UC IRB Office – The UC IRB Office is the administrative office for all University of Cincinnati Institutional Review Boards. Located at Wherry Hall, Room G-8, with hours of operation Monday through Friday 8:00 am – 5:00 pm. Telephone number 513-558-5259.

Office of Sponsored Programs (OSP) – The OSP is the UC department that is responsible for the final review, negotiation and submission of all grant and contract applications, and agreements. The OSP provides financial and other administrative assistance by preparing financial reports, submitting invoices, processing payments, and addressing other primary research administration functions. Located at 7148 One Edwards, with hours of operation Monday through Friday, 8:00 am – 5:00 pm. Telephone number is 513-556-2870.

UC Institutional Bio-safety Office - The Bio-safety Office assists facility and staff in observing safer biomedical laboratory practices as prescribed by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The office is the administrative office of the Institutional Bio-safety Committee (IBC). Located at Wherry Hall, Room G-3,with hours of operation being Monday through Friday 8:00am – 5:00 pm. Telephone number 513-558-5210.

CVAMC Radiation Safety Committee – The RSC monitors all research activities that use radioactive materials and equipment that produces radiation, or that occur in the vicinity of radioactive materials. Chair of the committee is Hiroshi Nishiyama, MD, Chief, Nuclear Medicine Service. G. Chris Rauf, is the RSC representative for the CVAMC Subcommittee for Research Safety. Mr. Rauf's telephone number is 513-475-6319.

General Clinical Research Center (GCRC) – The VA GCRC is a 3,000 square feet dedicated medical unit, designed to provide space, special research equipment, and experienced staff to support clinical investigators on the UC, VA and Cincinnati Children's Hospital campuses. Its overall mission is to provide a site for the study of adults with complex medical and/or psychiatric disorders. For information on any VA GCRC issues please contact Amelia Nasrallah, VA GCRC Administrator at 513- 558-2226.